three groups have been made, although it has been shown that erythrogenic toxin is not the same substance as streptolysin.[30] Groups A, C (human) and G strains all produce active fibrinolysins and streptolysins O, while strains belonging to the other groups do not.

The qualitative and quantitative relations between the streptolysins and the fibrinolysins produced by the three groups have been little studied, and most of the experiments have been performed with animals. Therefore, the studies made in connection with our patient, which suggest that the fibrinolysins and streptolysins O of groups A and C are similar, if not identical, are particularly interesting.

It can be said that hemolytic streptococci of groups C and G have certain characteristics in common with members of group A and that they may be equally capable of producing severe infections in human beings. It is only through continued correlation of careful clinical and laboratory observations, such as have been attempted in this study, that the role of the various Lancefield groups of hemolytic streptococci in infections in human beings will be finally determined.

SUMMARY AND CONCLUSIONS

A case of bacteremia caused by hemolytic streptococci of Lancefield group C is reported in which recovery followed administration of sulfadiazine. Some clinical features of the case are discussed, including the mechanism of recovery and the nature of the scarlatiniform rash.

The pertinent literature is reviewed, and the results of immunologic studies made in connection with this case are presented. The evidence suggests that the fibrinolysins and streptolysins O of groups A and C are similar, if not identical.

These findings are discussed in relation to the Lancefield groups as a whole, and it is pointed out that members of groups C and G have certain characteristics in common with members of group A and that they may be equally capable of producing severe infections in human beings.

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30. Todd, E. W.; Laurent, L. J. M., and Hill, N. G.: An Examination of the Relationship Between Streptococcal Antitoxin and Antistreptolysin, J. Path. & Bact. **36**:201, 1933.

PRIMARY AND SECONDARY HYPERPARATHYROIDISM

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GENERAL CONSIDERATIONS

In 1891 Recklinghausen [1a] described a curious disease of bone characterized by destruction and repair, marked softening of the bones and the presence of odd cysts. He recognized the similarity of his cases to that described by Engel [1b] some twenty-seven years previously. Recklinghausen was not aware of any endocrine disorder associated with the bony changes which he described. As a matter of fact, during the course of the next number of years many pathologists [2] noted tumors of the parathyroid glands in the presence of certain kinds of bone disease but failed to grasp the etiologic relationship between the two. Erdheim [3] was probably the first to recognize more than a casual relationship between the bony changes and the hyperplasia of the parathyroid glands in cases of osteomalacia, although his explanation of the observed phenomena later proved to be inadequate. It is easy to understand the early confusion of the pathologists. Hyperplasia of these glands had been observed in a variety of conditions. Thus MacCallum,[4] as early as 1905, reported enlargement of the parathyroid glands in chronic renal disease. Its presence in osteomalacia, rickets and Recklinghausen's disease was

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1. (*a*) von Recklinghausen, F., in Festschrift Rudolf Virchow zu seinen 71. Geburtstage, gewidmet von den früheren und jetzigen Assistenten des Berliner pathologischen Instituts, Berlin, G. Reimer, 1891. (*b*) Engel, G.: Ein Fall von zystoider Entartung des ganzen Skeletts, Inaug. Dissert., Giessen, F. C. Pietsch, 1864.

2. Dawson, J. W., and Struthers, J. W.: Generalized Osteitis Fibrosa with Parathyroid Tumor and Metastatic Calcification, Including a Critical Discussion of the Pathologic Processes Underlying Osseous Dystrophies, Edinburgh M. J. **30**:421, 1923.

3. Erdheim, J., cited by Biedl, A.: Innere Sekretion, ed. 2, Berlin, Urban & Schwarzenberg, 1913, pt. 1, p. 108.

4. MacCallum, W. G.: Tumor of the Parathyroid Glands, Bull. Johns Hopkins Hosp. **16**:87, 1905.

subsequently commented on. It was only after the isolation by Collip [5] of a potent extract of the parathyroid glands that the relationship between these diverse clinical conditions and abnormalities of the parathyroid glands was recognized. It was found that the histologic and chemical changes produced by parathyroid extract in the experimental animal were indeed very similar to the histologic and chemical changes observed in patients with tumors of these glands.

Certain things then became clear. The common denominators in the apparently unrelated conditions of chronic renal disease, osteomalacia, rickets, carcinomatous metastasis to the bones [6] and osteitis fibrosa cystica were the extensive bony changes, although these changes were dissimilar in the various conditions, and the abnormalities of the parathyroid glands, although these abnormalities also were different. One phenomenon, however, had been almost consistently observed and that was that when the bony changes were such as were described by Recklinghausen, a tumor of a parathyroid gland was almost always found, whereas in the other conditions all four parathyroid glands were usually hyperplastic.

The final crystallization of the pathologic distinction was provided by the work of Castleman and Mallory.[7] Employing their findings as a basis, they classified enlargements of the parathyroid glands into two groups—those due to tumor and those due to hyperplasia. Tumor usually affects one, rarely two parathyroid glands; the remaining parathyroid glands are perfectly normal grossly and histologically. When the pathologic enlargement of the parathyroid glands is due to hyperplasia, all four glands are usually involved. The enlargements in the latter group are further divided into primary and secondary. The primary hyperplasia produces actual primary hyperparathyroidism as described by Albright,[8] and the secondary, the hyperplasia which is usually associated with the presence of chronic renal disease, rickets, osteomalacia, multiple myeloma and Cushing's syndrome. The secondary hyperplasia occurs as a compensatory mechanism in response to the underlying disease. Perhaps it is worth while emphasizing that secondary hyperparathyroidism is a true hyperfunction of the parathyroid glands, although not amenable to therapy as is primary hyperparathyroidism.

5. Collip, J. B.: The Parathyroids, Medicine **5**:1, 1926.

6. Klemperer, P.: Parathyroid Hyperplasia and Bone Destruction in Generalized Carcinomatosis, Surg., Gynec. & Obst. **36**:11, 1923.

7. Castleman, B., and Mallory, T. B.: Pathology of the Parathyroid Glands in Hyperparathyroidism: Study of Twenty-Five Cases, Am. J. Path. **11**:1, 1935.

8. Albright, F.: Hyperparathyroidism Due to Idiopathic Hypertrophy of Parathyroid Tissue: Follow-Up Report on Six Cases, Tr. A. Am. Physicians **52**:171, 1937.

The use of a potent parathyroid extract [5] served to demonstrate the characteristic chemical changes which occur in hyperparathyroidism and which result in the classic bony changes. Greenwald and Gross [9] showed that the administration of parathyroid extract to dogs produced hypercalcemia with increased excretion of both calcium and phosphorus in the urine. The clinical picture of primary hyperparathyroidism then came into sharper focus, and in 1926 Mandl,[10] utilizing this information, operated on a patient with osteitis fibrosa cystica and found and removed an adenoma of the parathyroid glands. The brilliant clinical recovery which followed this operation was a temporary one, but it served to establish the entity of osteitis fibrosa cystica associated with tumor of the parathyroid glands on a firm clinical footing. Mandl in this patient demonstrated essentially the same phenomena that Greenwald and Gross found in their dogs. Before operation the urine showed excessive amounts of calcium, while after operation the calcium content fell to normal. In 1929 Albright and his co-workers [11] showed that the effects of parathyroid extract injected into man were similar to those in the dog. Somewhat earlier, Hueper [12] demonstrated that metastatic calcification occurred characteristically in the lungs, the gastric mucosa and the kidneys after the administration of excessive amounts of parathyroid extract to dogs. Bauer and his group [13] and Jaffe [14] reported decalcification of the skeleton resulting from long-continued administration of parathyroid extract.

If we were to summarize the clinical findings of primary hyperparathyroidism, we should find that they are essentially the same as those which follow prolonged administration of a parathyroid extract to dogs. There occur hypercalcemia, lowering of blood phosphate, increase

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9. Greenwald, I., and Gross, J.: The Effect of Thyroparathyroidectomy in Dogs upon the Excretion of Calcium, Phosphorus and Magnesium, J. Biol. Chem. **66**:185, 1925; The Effect of the Administration of a Potent Parathyroid Extract upon the Excretion of Nitrogen, Phosphorus, Calcium and Magnesium, with Some Remarks on the Solubility of Calcium Phosphate in Serum and the Pathogenesis of Tetany, ibid. **66**:217, 1925.

10. Mandl, G.: Klinisches und Experimentelles zur Frage der lokalisierten und generalisierten Ostitis fibrosa, Arch. f. klin. Chir. **143**:245, 1926.

11. Albright, F.; Bauer, W.; Ropes, W., and Aub, J.: Studies in Calcium and Phosphorus Metabolism: IV. The Effects of the Parathyroid Hormone, J. Clin. Investigation **7**:139, 1929.

12. Hueper, W.: Metastatic Calcifications in the Organs of the Dog After Injections of Parathyroid Extract, Arch. Path. **3**:14 (Jan.) 1927.

13. Bauer, W.; Aub, J. C., and Albright, F.: Studies of Calcium and Phosphorus Metabolism: V. A Study of the Bone Trabeculae as a Readily Available Reserve Supply of Calcium, J. Exper. Med. **19**:145, 1929.

14. Jaffe, H. L.: Hyperparathyroidism, Arch. Path. **16**:63 (July); 236 (Aug.) 1933.

in the calcium and phosphorus in the urine and decalcification of the bones. The marked increase in the calcium excreted in the urine can be utilized as a test for hyperfunction of the parathyroid glands, since the patient will excrete more calcium than he consumes and will be in negative calcium balance. The question as to whether there also occurs an increase in the calcium excreted in the stool in primary hyperparathyroidism is an interesting one. Albright and his co-workers [11] found that parathyroid extract exercised no effect on the fecal excretion of calcium in 8 patients, 4 with otosclerosis, 2 with chronic lead poisoning and 2 with ossifying hematomas. Bulger, Dixon and Barr,[15] however, in their classic paper on hyperparathyroidism, found that in 2 of their 3 cases there did occur an increase in the fecal excretion of calcium. The essential difference between the two groups is that one dealt with persons in whom the parathyroid glands were not directly implicated, the other with patients in whom there was definite hyperfunction of these glands. The site of the excretion of calcium is determined to a great extent by the availability of a particular route for the excretion of calcium. The factors which may determine this will be discussed in greater detail later. But, if for one or a number of different reasons, the amount of calcium which can be excreted in the urine is not adequate, as it may not be in chronic renal disease,[16] then an increase in the excretion of calcium and phosphorus into the gastrointestinal tract may result.

As was mentioned before, the causative agent of osteitis fibrosa cystica or primary hyperparathyroidism is usually an adenoma of a parathyroid gland. Occasionally there may be an adenoma of more than one parathyroid gland.[17] However, Allbright and his co-workers [8] described 6 cases of primary hyperparathyroidism associated with hypertrophy of the parathyroid glands in the absence of an actual tumor. Wilder [18] cited a case described by Dubois, Aub, Bauer and Richardson in which a patient presented all the classic signs and symptoms of hyperparathyroidism, including a negative urinary calcium balance. At opera-

15. Bulger, H. A.; Dixon, H. A., and Barr, D. P.: The Functional Pathology of Hyperparathyroidism, J. Clin. Investigation **9**:143, 1931.

16. (*a*) Halverson, J. O.; Mohler, H. K., and Bergeim, O.: The Calcium Content of the Blood Serum in Certain Pathological Conditions, J. Biol. Chem. **32**:171, 1927. (*b*) Scriver, W. de M.: Observations on the Excretion of Calcium in Two Cases of Nephrosis Treated with Parathyroid Extract, J. Clin. Investigation **6**:115, 1928. (*c*) Hetényi, G., and Nógráde, S. V.: Ueber die Kalkausscheidung der gesunden und kranken Niere, Klin. Wchnschr. **6**:1308, 1925.

17. Jaffe, H. L.: Hyperparathyroidism, Bull. New York Acad. Med. **16**:291 (May) 1940.

18. Wilder, R. M.: Hyperparathyroidism: Tumor of the Parathyroid Glands Associated with Osteitis Fibrosa, Endocrinology **13**:231 (May) 1929.

tion, however, no abnormalities were found. Two normal parathyroid glands were removed, and this was followed by a considerable improvement in the patient's condition. Wilder concluded that there can be hyperfunction of the parathyroid glands without either hypertrophy or tumor, and he drew an apt analogy to the hyperinsulinism occurring in the absence of an adenoma involving the islets of Langerhans. That this is a distinct possibility may well be true. But it should be remembered that a tumor may be present in an aberrant parathyroid gland located in the mediastinum and if not specifically and expertly looked for, it may very well be missed (note cases 1 and 2).

Patients with secondary hyperparathyroidism form a relatively large group, and one never finds an isolated adenoma of a parathyroid gland in these patients but, rather, hyperplastic glands with or without the characteristic bony and chemical changes, or the bony and chemical changes with histologically perfectly normal parathyroid glands. Secondary hyperparathyroidism may occur in patients with chronic renal disease, multiple myeloma, carcinomatous metastasis to the bones, Cushing's syndrome, rickets, osteomalacia and perhaps several other clinical conditions. The most common of these is chronic renal disease.

Bergstrand,[19] Hubbard and Wentworth,[20] Pappenheimer and Wilens,[21] Shelling and Remsen,[22] Shelling [23] and Anderson [24] have reported excellent studies on the relation of chronic renal disease to hyperparathyroidism. The characteristic picture is that observed in a patient with long-standing renal disease and chronic acidosis in whom extensive bony changes have developed. The blood calcium is usually normal but may be either depressed or elevated. The blood phosphorus, however, is almost always elevated. Studies of the calcium balance usually yield results similar to those obtained in a patient with primary hyperparathyroidism. Roentgenographic studies of the skeleton generally show extensive decalcification of bony structures and not infrequently metastatic calcification in various other parts of the body. The parathyroid glands may be markedly hyperplastic. The clinical distinc-

19. Bergstrand, H.: Parathyroideastudien: II. Ueber Tumoren und hyperplastische Zustände der Nebenschilddrüsen, Acta med. Scandinav. **54**:539, 1921.

20. Hubbard, R. S., and Wentworth, J. A.: A Case of Metastatic Calcification Associated with Chronic Nephritis and Hyperplasia of the Parathyroids, Proc. Soc. Exper. Biol. & Med. **18**:307, 1921.

21. Pappenheimer, A. M., and Wilens, S. L.: Enlargement of the Parathyroid Glands in Renal Disease, Am. J. Path. **11**:73, 1935.

22. Shelling, D. H., and Remsen, D.: Renal Rickets, Bull. Johns Hopkins Hosp. **57**:158, 1935.

23. Shelling, D. H.: The Parathyroids in Health and Disease, St. Louis, C. V. Mosby Company, 1935.

24. Anderson, W. A. D.: Hyperparathyroidism and Renal Disease, Arch. Path. **27**:753 (April) 1939.

tion between primary hyperparathyroidism and chronic renal disease with secondary hyperparathyroidism is frequently quite difficult. It must be remembered that in Recklinghausen's disease recurrent renal calculi may occur, which can produce extensive renal damage. In these instances, chronic renal failure may develop, which may produce a distortion of the characteristic chemical findings in the blood. One sees the combination of a well defined adenoma of a parathyroid gland with hyperplasia of the remaining parathyroid glands. Such a case was described by Downs and Scott [25] and such an instance is included in our group (case 3). In these cases it is possible to postulate that the chronic renal failure resulting from the adenoma of the parathyroid gland has induced, in turn, hyperplasia of the other parathyroid glands.

The question arises as to why hyperplasia of the parathyroid glands develops in patients with chronic renal insufficiency. We know that the chronic renal disease and the chronic acidosis precede the glandular hyperplasia. Bony changes, notably decalcification,[26] have been described in chronic renal failure, while acidosis is not infrequently associated with increase in the urinary calcium output.[15] Perhaps the increase in the urinary excretion of calcium under such circumstances occurs because the ability of the kidneys to form ammonia is impaired. In any event, while calcium is excreted in the urine in excessive or in adequate amounts, phosphate is retained. It is a moot point whether the parathyroid glands are concerned primarily with the metabolism of calcium or with that of phosphorus. Since the two ions enjoy a reciprocal relationship, expressed essentially by the equation $[Ca^{++}]^3 \times [PO_4^{\equiv}]^2 = K$, it is questionable whether one can distinguish a primary effect on either of these ions. However, Albright and his co-workers [11] expressed the opinion that the primary effect of parathyroid extract is on the metabolism of phosphorus rather than on that of calcium. This apparently was the view of Shelling and Remsen, too.[22] Albright contended that parathyroid extract causes primarily an increase in the urinary excretion of phosphorus with resulting hypophosphatemia. Because of the lowered level of serum phosphorus, the serum is less saturated with calcium phosphate, and consequently there is an increased tendency for calcium phosphate to enter the blood, either from the bones or from the gastrointestinal tract. This produces hypercalcemia and secondarily hypercalciuria.

25. Downs, R. S., and Scott, V.: Hyperparathyroidism with Adenoma Causing Renal Failure and Secondary Hyperparathyroidism, Arch. Int. Med. **67**:658 (March) 1941.

26. Ginzler, A. M., and Jaffe, H. L.: Osseous Findings in Chronic Renal Insufficiency in Adults, Am. J. Path. **17**:292, 1941.

The proponents [27] of the other theory held that parathyroid extract acts on bone tissue to dissolve and liberate calcium phosphate. This causes hypercalcemia, hypercalciuria and hyperphosphaturia. But, as Albright rightly pointed out, some secondary mechanism is required to explain the hypophosphatemia.

It would be pointless for us to become involved in a review of the extensive arguments and experimental evidence which have accumulated concerning these two hypotheses. Clinically, we shall assume that the parathyroid glands are concerned with the metabolism of calcium and phosphorus, particularly with the mechanism of the excretion of these ions.

Occasionally one finds instances of both renal rickets and primary hyperparathyroidism in which the excretion of calcium in the urine is reduced. In these instances studies of the calcium balance performed on the urine will not yield the characteristic results. Snapper [28] attempted to explain this on the basis of vitamin D deficiency. S. H. Liu and his co-workers, quoted by Snapper,[28] found that in vitamin D deficiency urinary excretion of calcium is diminished, although the blood calcium may be normal or even elevated. This explanation, however, probably does not hold for the patients with hyperparathyroidism seen in this country. The reduced urinary excretion of calcium occurs only in instances in which there is present extensive renal damage, and it is the latter factor which probably determines the reduction of the urinary calcium output. This hypothesis received experimental confirmation in the work of Halverson and his co-workers,[16a] that of Scriver [16b] and that of Hetényi and Nógráde.[16c]

One of the interesting phenomena occasionally observed both in primary hyperparathyroidism complicated by renal impairment and in secondary hyperparathyroidism due to renal disease is that of diffuse metastatic calcification. The presence of metastatic calcific deposits represents precipitation of calcium phosphate. The solubility of calcium phosphate is made possible and is also limited by certain physicochemical relationships, such as the p_H of the solvent medium, the carbon dioxide tension, the protein concentration and finally the total electrolyte concentration of the medium. These factors which determine the degree of solubility of calcium phosphate in the serum also determine its solubility in other mediums, such as the urine and perhaps the tissues. When the factors mentioned are kept constant, the solubility of calcium phosphate is constant, that is $[Ca^{++}]^3 \times [PO_4^{\equiv}]^2 = K$. In hyperparathyroidism

27. Thompson, D. L., and Collip, J. B.: The Parathyroid Glands, Physiol. Rev. **12**:309, 1932. Jaffe.[14]

28. Snapper, I.: Different Features of the Syndrome of Hyperparathyroidism, Acta med. Scandinav. **103**:321, 1940.

there may be a disturbance in this relationship. This will happen particularly in the presence of extensive renal disease. In the absence of such renal disease the elevation of the blood calcium is compensated for by increased excretion of phosphorus in the urine above that of calcium, so that the product of the calcium and the phosphorus concentration remains constant. When renal failure occurs, however, and the urinary excretion of phosphorus is reduced, the relationship between the calcium and the phosphate ions is altered, both in the urine and in the blood. In addition, the other factors which govern the solubility of the calcium are also changed. As a result, the degree of solubility of calcium phosphate is changed in these mediums. Such alterations in the factors governing the solubility of the calcium probably determine precipitation of calcium phosphate in the tissues. In this respect it is interesting to note that deposits of calcium occur particularly in the lungs, the gastric mucosa and the kidneys, organs in which the hydrogen ion concentration may vary considerably from that of the blood.

CLINICAL CONSIDERATIONS

The symptoms of primary hyperparathyroidism may be roughly divided into two large groups: the general symptoms, such as weakness, lassitude, anorexia, loss of weight, diffuse aches and pains and others, and the specific symptoms, that is, those referable to the genitourinary tract, the skeletal system and the hypercalcemia. The genitourinary symptoms are those associated with recurrent renal calculi. Probably 30 to 40 per cent of the patients with primary hyperparathyroidism have evidence of the presence of urinary calculi at some time or other during the course of the disease. Not infrequently the first evidence of the illness is the presence of such stones. Of 17 cases presented by Albright and his group,[29] 8 were discovered during routine determinations of the blood calcium in patients with urinary lithiasis. In 3 of the 5 cases included in our group of Recklinghausen's disease urinary calculi were found. Such stones may appear years before any other signs of hyperparathyroidism are present. Not infrequently, the calculi are bilateral. The evidence of progressive renal failure so often seen in patients with primary hyperparathyroidism occurs in these patients with renal calculi. Deposition of calcium may also occur in the renal substance itself.

In instances in which renal calculi have produced impairment of renal function, there may occur a distortion of the characteristic chemical findings in the blood usually seen in Recklinghausen's disease. In these instances the blood phosphorus may be elevated and the urinary calcium

29. Albright, F.; Aub, J. C., and Bauer, W.: Hyperparathyroidism: Common and Polymorphic Condition as Illustrated by Seventeen Proved Cases from One Clinic, J. A. M. A. **102**:1276 (April 21) 1934.

reduced. This group is particularly difficult to distinguish from instances of renal rickets, and the most helpful aid in the differentiation lies in eliciting a careful history of the onset of the disease. The prognosis in this group is usually poor despite the successful removal of an adenoma of a parathyroid gland, since the patient may succumb to progressive renal failure. It is imperative to diagnose primary hyperparathyroidism before irreversible changes in the kidneys have occurred.

The skeletal changes in primary hyperparathyroidism may be manifested by spontaneous fractures, lumps, usually of the extremities, the ribs and the clavicles, and soft tumors of the jaw, diagnosed as epulides. There may be marked deformities and a considerable reduction in height of the patient, and in extreme involvement, distortion of the bones in all directions. Patients with the disease in this form are less commonly seen today, probably because physicians are more aware of the possibility of hyperparathyroidism, and the disease is therefore recognized earlier. Pathologically, the most outstanding change in the bones is the generalized demineralization. Later there occur cysts, giant cell tumors, osteoclasts and osteoblasts and large deposits of fibrous tissue. In this disease, then, resorptive and reparative processes go on simultaneously, so that in place of the original bone and marrow spaces there are present fibrous tissue, abundance of osteoclasts and osteoblasts and some new bone. The destruction of bone, however, exceeds the formation of new bone. Roentgenologically, the decalcification and the cyst formation are easily evident, and usually the entire skeleton is involved in one way or another to varying degrees. In simple neoplastic metastasis to bones there are areas which appear entirely normal in roentgenograms in contrast with the metastatically involved areas. This lack of universal involvement in the latter condition helps to distinguish roentgenologically between the two.

The symptoms usually associated with the hypercalcemia of primary hyperparathyroidism are polyuria, polydypsia, muscular atony, bradycardia and occasionally cardiac irregularities.

The characteristic metabolic chemical changes consist of hypercalcemia, hypophosphatemia, hypercalcinuria, hyperphosphaturia and a considerable increase in the blood phosphatase. In addition, the patients usually have a negative urinary calcium balance; that is, the excretion of calcium is considerably in excess of the intake.

It must be remembered that the chemical findings just enumerated need not, and indeed do not, occur in all cases. This is particularly true in the presence of impaired renal function.

The treatment of primary hyperparathyroidism is always surgical. When the renal damage and the skeletal changes are not too extensive, the ultimate outlook for the patient is good. Recalcification of the bones will eventually occur, although the cysts will remain essentially unaffected.

In exploring for the presence of an adenoma of the parathyroid glands, it should be remembered that one or more of these glands may be aberrant and may be located in the superior mediastinum. No surgical exploration is complete unless all four of the glands have been visualized. Although, generally speaking, only one gland is adenomatous, occasionally more may be involved.

Following parathyroidectomy, there will occur a prompt drop in the blood calcium, so that within twenty-four hours it may have returned to normal or even fallen to tetanic levels. The blood phosphorus does not increase for several days, while the blood phosphatase may stay elevated for many months or even years.[30]

The onset of tetany after operation is not uncommon and may occur at any time within the first two weeks. When tetany occurs within the first twenty-four hours, it is not infrequently associated with a normal level of blood calcium but a level which is considerably lower than that present preoperatively. Tetany which appears after several days is always associated with blood calcium values which are at tetanic levels. The postoperative tetany may be due to one of several factors. The most important perhaps is functional atrophy of the normal parathyroid glands. After removal of the tumor, the remaining parathyroid glands will in time resume their normal function, but until such time tetany may appear and supportive treatment be indicated. Another common cause of postoperative tetany is the removal of too much parathyroid tissue. This usually occurs in those instances in which more than one exploratory operation has been performed before a tumor is found and removed, normal parathyroid glands being removed in the preliminary operations. The tetany which results in these instances is of a permanent character. Finally, tetany may follow a precipitate postoperative drop in the blood calcium. The tetanic manifestations may appear despite the fact that the blood calcium value is practically normal.

The treatment of postoperative tetany is essentially the same as that of spontaneous tetany. Calcium is administered by mouth and parenterally, the chloride and gluconate being used intravenously. The latter may be used intramuscularly and subcutaneously. The mild tetanic manifestations are readily controlled with the aid of calcium alone, particularly when this is given intramuscularly or intravenously. The more severe manifestations, however, require in addition the use of solution of parathyroid or of dihydrotachysterol. Solution of parathyroid[30a]

30. Gutman, A. B.; Tyson, T. L., and Gutman, E. B.: Serum Calcium, Inorganic Phosphorus, and Phosphatase Activity in Hyperparathyroidism, Paget's Disease, Multiple Myeloma and Neoplastic Disease of the Bones, Arch. Int. Med. **57**:379 (Feb.) 1936.

30a. The preparation used in the cases reported was one meeting the standards for solution of parathyroid U. S. P.

may be given intravenously or subcutaneously; dihydrotachysterol, however, may be used orally only. The dose of solution of parathyroid varies with the intensity of the symptoms. Although usually a dose yielding 10 to 20 parathyroid units several times a day is adequate, much larger doses may be given with safety. Dihydrotachysterol is given in doses of 1 to 2 cc. of a 0.5 per cent solution in oil three times a day during the period of severe tetany. The danger of overdosage with either of these products lies in the development and persistence of hypercalcemia, with increase in the urinary excretion of calcium and phosphorus.

The postoperative treatment of hyperparathyroidism other than the treatment of tetany is important. Large amounts of calcium are required for remineralization of the bones, and the patients show a remarkable avidity for calcium. This is well shown in a case in the series reported by Bulger, Dixon and Barr,[15] in which 350 Gm. of calcium and 180 Gm. of phosphorus were stored over a period of approximately ten months. Calcium thus stored is probably used for recalcification of the skeleton. Consequently, it is important to give the patients daily supplementary amounts of calcium by mouth in addition to that which they normally consume in their diets. In this respect, it is important to remember to avoid an excessive intake of phosphate. With such an intake, calcium will be used to precipitate the excess phosphate as calcium phosphate into the large bowel.

In addition to the daily 3 to 5 Gm. of a calcium salt, it is desirable to give small amounts of vitamin D. The latter increases the absorption of calcium from the intestinal tract and helps to divert the calcium to the bones. An excess of vitamin D, however, should be avoided, since parathyroid hypoplasia may result.

REPORT OF CASES

Cases of Primary Hyperparathyroidism

CASE 1.—B. K., a white woman 47 years of age, was admitted to the hospital for the first time in November 1932. At that time she complained of pain in the lower part of the back, dysuria, diurnal and nocturnal urinary frequency, fatigue and weakness of ten days' duration. Ten years prior to this, she had similar complaints, which subsided after several days. On investigation in the hospital, the only positive findings were a palpable left kidney, blood urea nitrogen amounting to 20 mg. per hundred cubic centimeters and blood pressure varying from 160 systolic and 90 diastolic to 170 systolic and 100 diastolic. Unfortunately, the blood calcium and phosphorus were not determined at that time.

The patient was then lost sight of until 1934, when she was readmitted with acute bronchopneumonia. When she recovered from this, her renal status was again investigated. Both kidneys were now palpable, and renal roentgenograms revealed bilateral dendritic calculi. There was marked impairment of renal function as measured by the phenolsulfonphthalein and urine concentration tests. The blood urea nitrogen amounted to 41 mg. per hundred cubic centimeters, while the blood calcium varied from 11.4 to 12.5 mg. and the blood phosphorus from 3.2 to 3.7 mg. per hundred cubic centimeters.

The patient was admitted to the hospital for the third time in November 1939, complaining of pain in the left flank, weakness and hematuria of three weeks' duration. On physical examination, it was found that her blood pressure had increased to 190 systolic and 100 diastolic and that she had definite masses in both flanks. Roentgenograms of the kidneys showed bilateral renal calculi, while roentgenograms of the skeletal structure showed irregular absorption of the trabeculae of the long bones, areas of rarefaction and increased density in the skull, cyst formation in the ribs and calcification of the pelvic vessels. The blood calcium now varied from 10.4 to 11.9 mg. and the phosphorus from 4.5 to 5.6 mg. per hundred cubic centimeters. The blood phosphatase was 44 King-Armstrong units, and the urea nitrogen varied from 28 to 60 mg. per hundred cubic centimeters.

The possibility of a parathyroid tumor was now seriously entertained, but surgical exploration of the neck failed to reveal any abnormal parathyroid glands, although only three were visualized.

The patient was again admitted to the hospital in August 1940, because of a fracture of the neck of the right femur. The blood calcium now varied from 11.0 to 13.0 mg. and the phosphorus from 4.0 to 8.4 mg. per hundred cubic centimeters. The blood phosphatase varied from 22 to 82 King-Armstrong units, and the urea nitrogen constantly mounted. Several months after this final admission the patient died in uremia.

On postmortem examination an adenoma of a retrosternal parathyroid gland was found, which weighed 12 Gm.

Comment.—There are several points which stand out sharply in this case. They are: the duration of the illness, which was approximately nine years; the predominant renal clinical picture with the formation of calculi; the observation that the blood calcium, although elevated, was not unduly so, while the phosphorus, even in the early stages of the disease, was not strikingly low, and the exploratory operation which failed to reveal the adenoma because the involved gland was retrosternal. When renal failure became well advanced, it was impossible to determine whether the hyperparathyroidism was primary or secondary to the disease of the kidneys. The discovery of an adenomatous parathyroid gland, in addition to the three normal glands, and the calculous character of the renal disease on postmortem examination finally revealed this case to be one of true primary hyperparathyroidism.

CASE 2.—I. V., a white woman 34 years of age, was admitted to the hospital in February 1934, complaining of urinary incontinence and diurnal and nocturnal frequency of four months' duration. Two years previously she had had similar symptoms, which were corrected after anterior and posterior colporrhaphy. During the present stay in the hospital, roentgen studies of the pelvis showed coarsening of the trabeculae of the innominate bones and of the head of the femur, as well as areas of increased density and smaller areas of transparency. These roentgen findings were interpreted as suggesting Paget's disease, although the blood calcium varied between 11.9 and 13.8 mg. and the phosphorus between 3.0 and 3.1 mg. per hundred cubic centimeters. The blood phosphatase was 70 King-Armstrong units.

The patient was readmitted to the hospital seven months later because of recurrent attacks of pain in the right side of the chest anteriorly, of sixteen days' duration. On examination, it was found that she had asymmetry and tremors of the tongue, hyperalgesia of the left side of the back corresponding to dorsal segments 7 to 10, marked tenderness over the middorsal region of the spinal column and a stocking type of hypoalgesia of the entire left leg. Roentgenologi-

cally, there was compression of the third, fourth, fifth and eleventh dorsal vertebrae, the facial bones showed thickening and irregular mottling due to partial absorption of calcium, the skull showed changes suggestive of Paget's disease and the right femur now showed several cysts. The blood calcium varied between 12.2 and 13.4 mg., and the phosphorus had decreased to 2.2 mg. per hundred cubic centimeters. The blood phosphatase was 47 King-Armstrong units.

In January 1936, one and one-half years after the last admission, the patient was readmitted to the hospital, complaining of headache, vomiting and pain in the epigastrium radiating to the back, of one week's duration. It was now found that her head had grown considerably larger and that considerable kyphosis of the upper dorsal part of the spinal column had developed, with slight scoliosis. The roentgen appearance of the skeleton was essentially as before, and roentgenologically it was impossible to determine whether the evident changes were due to hyperparathyroidism or to Paget's disease. On Feb. 11, 1936, a biopsy of the greater trochanter of the right femur was reported to have shown changes typical of osteitis fibrosa cystica. The blood calcium on this admission varied between 11.8 and 13.5 mg. and the phosphorus between 2.6 and 3.3 mg. per hundred cubic centimeters. The blood phosphate was 134 King-Armstrong units. A study of calcium balance was made for the first time during this period and showed a strongly negative calcium balance. With a total calcium intake over a three day period of 300 mg., she excreted 1,050 mg. of calcium in the urine during this same period.

It was now evident that the patient had hyperparathyroidism. On Feb. 18, 1936, she was operated on, but no abnormal parathyroid glands were found.

In November 1938 she was reinvestigated. She had lost over 30 pounds (13.5 Kg.) in weight since the last admission. There was a decrease in height of 3½ inches (8.9 cm.). The left femur was bowed and thickened, as was the right ulna. The skull had increased markedly in size. The blood calcium was 12.0 mg. and the phosphorus 2.9 mg. per hundred cubic centimeters. The blood phosphatase was 140 King-Armstrong units. The result of a study of calcium balance was even more striking: With an intake of 300 mg. over a three day period, she excreted 1,300 mg. of urinary calcium. A second exploratory operation revealed a large adenoma of a parathyroid gland in the mediastinum. This was successfully removed.

The patient was seen in October 1939 and in April 1940. She felt quite well but had continued to decrease in height. Roentgen studies of the long bones and of the skull showed increased density in the previous areas of rarefaction but also gave considerable evidence suggestive of Paget's disease. The blood calcium amounted to 9.1 and 10.4 mg. and the phosphorus 3.9 and 4.1 mg. per hundred cubic centimeters. The blood phosphatase had fallen to 80 King-Armstrong units.

Comment.—This case is of particular interest because it involved differentiation between Paget's disease and hyperparathyroidism. Generally speaking, with the aid of laboratory and roentgen findings the two conditions can be clearly distinguished. In this patient both conditions were apparently present, evidenced by the continued decrease in height and the increase in the size of the skull after a successful operation. This case is of further interest because of the mediastinal location of the adenomatous parathyroid gland.

Case 3.—E. P., a white man 42 years of age, was admitted to the hospital for the first time in June 1938. He complained of lassitude and fatigue and of anorexia of five years' duration. For several months prior to admission he had experienced pains "all over the body," and during the past two months he had

noticed a tumor of the left lower jaw. Five years prior to his admission to the hospital a calculus had been removed from the urinary bladder, and for the past two years he had had recurrent epulides.

On investigation in the hospital, it was found that he had a soft tumor of the left lower jaw. The blood calcium was 14.0 mg., while the phosphorus was 3.3 mg., per hundred cubic centimeters. The phosphatase was 53 King-Armstrong units. The blood urea nitrogen amounted to 29 mg. per hundred cubic centimeters. A study of calcium balance yielded the following result: With a calcium intake of 100 mg. daily over a three day period, the patient excreted 902 mg. of calcium in the urine. Roentgen studies of the skeleton showed diffuse decalcification. Cysts were present in the left and right radiuses and ulnas, in the ischia, the left fibula, the right tibia and the right humerus.

It was evident on the basis both of clinical and laboratory studies that this patient had hyperparathyroidism. Consequently, on June 30, eight days after his admission to the hospital, he was operated on and four enlarged parathyroid glands were found, two of which (the left superior and the right inferior) were excised. Microscopic study of the removed glands showed the presence of a chief cell adenoma of one of them, with some hyperplasia of the oxyphilic and clear cells of the other.

Following the operation, the blood calcium fell progressively to 11.4 mg. per hundred cubic centimeters, while the phosphorus remained essentially unchanged. Another study of the calcium balance just prior to his discharge from the hospital showed marked reduction in the excretion of calcium, so that with an intake of 300 mg. of calcium over a three day period he now excreted only 495 mg. Studies of the urine during this period showed the specific gravity fixed at 1.012, with a trace of albumin, 2 to 4 red blood cells per high power field and occasional casts. The blood pressure was never elevated.

The patient was admitted to the hospital for the second time in October 1939, approximately fifteen months after the first admission. He continued to complain of weakness, fatigue and pains, particularly of the knees and the elbows. In addition, he had noticed a recurrence of the tumor of the jaw which had been previously removed. The blood calcium had again increased to 13.1 mg., while the blood phosphorus was 3.1 mg. and the urea nitrogen was 13 mg. per hundred cubic centimeters. The blood phosphatase was still elevated to 48 King-Armstrong units. The test for excretion of calcium showed only slight improvement over the previous result. Over a three day period he excreted a total of 417 mg. of calcium in the urine following a total intake of 300 mg. of calcium. Roentgenograms of the bony structure showed relatively little improvement since his last admission to the hospital. The renal function continued to show marked impairment. The specific gravity was still fixed at 1.012, and the urea clearance was 43 per cent of normal, while the phenolsulfonphthalein test showed 15 per cent excretion in four hours. It was decided to operate again, and the remaining right parathyroid gland and over one-half of the remaining left parathyroid gland were removed.

On October 30, eight days after the operation, the blood calcium had fallen to 9.2 mg., while the blood phosphorus had increased to 4.5 mg. per hundred cubic centimeters. Approximately two weeks after the operation, tingling and quivering of the extremities developed. The deep reflexes were hyperactive. He had marked bilateral ankle clonus and a Chvostek sign. The blood calcium at this point was 5.6 mg., the phosphorus 4.8 mg. and the urea nitrogen 30 mg. per hundred cubic centimeters, and the carbon dioxide–combining power was 50.5 volumes per cent. It was evident that the patient had tetany. He was treated with calcium gluconate

intravenously and given a low phosphorus, high calcium diet and dihydrotachysterol. Improvement was fairly prompt, although not striking in extent. The blood calcium increased to 8.3 mg. and the phosphorus dropped to 3.6 mg. per hundred cubic centimeters. He was discharged from the hospital for ambulatory treatment. Microscopic study of the excised parathyroid glands showed diffuse hyperplasia of all cell types.

In March 1940, four and one-half months after the onset of the tetanic episode, the patient felt quite well. He continued to take calcium lactate and viosterol. The blood calcium was 10.2 mg. and the phosphorus 3.6 mg. per hundred cubic centimeters. If the taking of calcium lactate was discontinued for any length of time, he experienced tingling of the lips and hands. Roentgen studies of the long bones showed considerable recalcification. The weakness and lassitude of which he complained had improved markedly.

Comment.—There are several interesting features about this case. The patient presented a fairly classic picture of primary hyperparathyroidism. He had no previous history of nephritis, although at the time of investigation in the hospital there was evidence of marked impairment of renal function. This may be explained, however, on the basis of previous renal calculous disease, since a stone had been removed from the urinary bladder five years previously. On operation, however, he had an adenoma of one parathyroid gland and hyperplasia of the remaining parathyroid glands, the former almost always seen in primary hyperparathyroidism. It is entirely possible that the hyperplasia of the parathyroid glands was secondary to the long-standing renal disease, while the latter was initially induced by the adenoma of the parathyroid gland (primary hyperparathyroidism) with formation of renal calculi.

After removal of the excessive parathyroid tissue, there occurred a considerable degree of improvement in the bony structure, although renal function continued to be seriously impaired. This is not entirely unexpected, since one would assume that the renal damage induced by the stones would be of an irreversible character. The tetany which developed was due to the excessive removal of parathyroid tissue.

Case 4.—R. T., a white woman 36 years of age, was admitted to the hospital for the first time in September 1936. She complained of attacks of pain in the right flank, radiating to the lower right abdominal quadrant and to the right thigh. The first such attack occurred four years prior to admission, and recurrent attacks appeared at approximately yearly intervals. She had no complaints referable to the bony structure at this time. Investigation in the hospital revealed the presence of bilateral renal calculi, and roentgen studies of the skeletal structure demonstrated the presence of some cystic changes in the left ilium. The skull and the long bones, however, were roentgenologically normal. The blood calcium varied from 11.8 to 13.0 mg. and the phosphorus from 3.5 to 4.0 mg. per hundred cubic centimeters. The total protein was 7.5 Gm. per hundred cubic centimeters, and the blood phosphatase was 8 King-Armstrong units. Three day study of the calcium balance performed on two separate occasions showed the total urinary calcium excreted to be 1,070 and 1,332 mg., respectively, with a total calcium intake of 300 mg. Studies of renal function gave essentially negative results. The patient was discharged from the hospital for further observation in the outpatient department.

She was readmitted to the hospital in April 1937. She then complained of generalized aches and pains, particularly over the left scapula. The blood calcium was 11.6 mg. and the phosphorus varied from 3.4 to 4.0 mg. per hundred cubic

centimeters. The blood phosphatase was 34 King-Armstrong units. Tests of renal function gave essentially normal results, and the urea nitrogen amounted to 13.0 mg. per hundred cubic centimeters. Roentgen studies of the bony structure showed little change in the cystic formation in the left ilium and equivocal slight decalcification of the long bones. On April 30 she was operated on and a tumor of the right inferior parathyroid gland was found. The pathologic report revealed the tumor to be a chief cell adenoma. Five days after operation, signs and symptoms of mild tetany developed. The blood calcium at this time amounted to 8.5 mg. per hundred cubic centimeters. She responded promptly to solution of parathyroid and calcium, and after a few days this therapy could be discontinued.

From the time of the operation until August 1939, when she was lost sight of, she continued to complain of diffuse aches and pains. The blood calcium now varied from 9.2 to 9.8 mg. and the phosphorus from 5.0 to 5.4 mg. per hundred cubic centimeters. The blood phosphatase was 15 King-Armstrong units. Tests of renal function still gave normal results, and the blood urea nitrogen amounted to 14 mg. per hundred cubic centimeters. Intravenous pyelograms were fairly normal. Roentgen studies of the skeletal system showed no essential change from the results of the previous investigation. It must be emphasized, however, that at no time were the bony changes particularly striking.

Comment.—This case is of interest because the predominant findings were recurrent renal calculi. The bony changes were always minimal, although the patient apparently had hyperparathyroidism for at least six years before operation.

CASE 5.—D. F., a white woman aged 54, was admitted to the hospital in March 1939. She complained of generalized aches and pains of twenty-one years' duration, decrease in height of 2 inches (5 cm.) during the past two years, loss of 40 pounds (18 Kg.) during this period, inability to walk because of severe pains in the legs of eight months' duration, and polyuria and polydypsia for the past half year. It is interesting that fifteen years before, on the basis of roentgen studies of the skull, she was suspected of having Paget's disease. Seven years before, she was found to have hypertension (190 systolic and 100 diastolic). Two years before, she was investigated in a hospital in California. During this study the blood calcium was found to be 8.5 mg., the phosphorus 4.2 mg. and the urea nitrogen 38 mg. per hundred cubic centimeters. Roentgenograms of the skeleton showed diffuse osteoporosis. She suffered from moderate secondary anemia, the hemoglobin being 55 per cent and the red blood cell count 3,400,000. The urine showed albumin and casts. It was felt that she had chronic diffuse glomerular nephritis with secondary hyperfunction of the parathyroid glands.

On her admission to the hospital in March 1939, roentgen studies of the bones showed two large cysts in the fifth and sixth ribs on the left side, spontaneous fracture of the fifth rib, fibrocystic changes of the left ilium and osteoporosis of the dorsal part of the spinal column, the skull, the pelvis and the femur. The blood calcium was found to be 13.5 and 13.2 mg. and the phosphorus 3.6 and 3.8 mg. per hundred cubic centimeters. The urea nitrogen amounted to 38 mg. per hundred cubic centimeters and the blood phosphatase to 76 King-Armstrong units. The blood pressure was 130 systolic and 80 diastolic, and the test of urine concentration showed inability to concentrate above 1.014 and fixation of the specific gravity between 1.010 and 1.014. The urine showed a small amount of albumin and an occasional cast.

Because of the elevation of the blood calcium in the presence of chronic renal disease, it was felt that this patient had primary hyperparathyroidism. An explora-

tory operation was therefore made, and an adenoma of the left lower parathyroid gland was excised. The remaining parathyroid glands appeared to be fairly normal in size.

Two days after operation the blood calcium fell to 8.4 mg. and two days later to 7.3 mg. per hundred cubic centimeters. The blood phosphorus remained at 3.3 mg. per hundred cubic centimeters. Directly after the operation oliguria developed. The urea nitrogen rose to 69 mg. per hundred cubic centimeters, and the carbon dioxide content fell to 29 volumes per cent. She was treated with solution of parathyroid, calcium, transfusions and alkalis. On the eighth postoperative day she contracted pneumonia, and on the tenth postoperative day she died.

Comment.—This case is of interest because it once again demonstrates the chronicity of the disease. In all probability, the changes of the skull diagnosed roentgenologically as Paget's disease fifteen years before were the early changes of hyperparathyroidism. This patient presented evidence of marked renal failure. Because of this, the diagnosis of renal rickets was entertained. However, the considerable elevation of the blood calcium and the normal level of the blood phosphorus pointed sharply to primary hyperparathyroidism.

Cases of Hyperparathyroidism Secondary to Multiple Myeloma and Carcinomatous Metastasis to the Bones

Case 6.—C. B., a white woman of 68 years, was admitted to another hospital for the first time in December 1939. At that time she complained of pain and weakness of the left arm of several months' duration. Roentgenograms of the skeletal structure showed a cyst of the left humerus and considerable decalcification of the long bones. The blood calcium amounted to 14.2 mg. and the phosphorus to 2.4 mg. per hundred cubic centimeters. The blood and urine were otherwise found to be completely normal. She had a small, firm, rounded mass in the right lobe of the thyroid gland. It was felt that she had hyperparathyroidism and that an exploratory examination should be made. At operation all four parathyroid glands were visualized and found to be entirely normal in size. The right lobe of the thyroid gland was removed, and the small palpable mass was found to be an adenoma. The parathyroid glands removed with the thyroid tissue were studied histologically and found to be normal.

The patient was fairly well after operation for a period of several months; then she began to complain of pains in the back, the chest and the long bones. She now had marked anorexia, weakness, dyspnea and cough. She was admitted to the Mount Sinai Hospital in April 1941. Roentgen studies at this time showed innumerable areas of destruction in the cranial and facial bones and the long bones. There was extensive osteoporosis of the dorsal and lumbar vertebrae, with collapse of several dorsal vertebrae. The blood calcium was now 12.0 mg. and the phosphorus 3.7 mg. per hundred cubic centimeters. The phosphatase amounted to 6 King-Armstrong units. The urine showed Bence Jones protein and a sternal puncture showed innumerable plasma cells.

The diagnosis of multiple myeloma was now definite, and it was evident that the original early changes in the bones, the elevation of the blood calcium and the depression of the phosphorus were due to hyperparathyroidism secondary to this malignant disease. It is interesting to note that these changes were not associated with any evident changes either in the size or in the histologic appearance of the parathyroid glands. The blood phosphatase was normal, as it usually is in cases of multiple myeloma, in contrast with cases of carcinomatous metastasis to the

bones, in which the blood phosphatase is frequently elevated.[30] This is by no means a hard and fast rule, however. Rowntree[31] reported instances of multiple myeloma with increased values for blood phosphatase.

CASE 7.—K. S., a white woman aged 39, was admitted to the hospital in April 1941, complaining of severe pains across the lower part of the back and shooting pains over the lateral and anterior aspects of the right thigh. These pains had been present for approximately one month. Roentgen studies revealed the presence of a compression fracture of the fourth lumbar vertebra with marked decalcification of this vertebra. In addition, there was marked decalcification of the entire dosal part of the spinal column and of the right innominate bone. There was an ovoid area of decreased density of the right iliac crest, and there was a fracture of the sixth rib. The blood calcium varied from 13.2 to 17.8 mg. and the phosphorus from 3.7 to 5.3 mg. per hundred cubic centimeters. It is interesting that of eight determinations of blood calcium only one showed 13.2 mg. per hundred cubic centimeters; the remaining seven determinations showed amounts that varied from 15.4 to 17.8 mg. The blood phosphatase, which on admission was 9 King-Armstrong units, rapidly increased to 60 King-Armstrong units within six weeks. The blood urea nitrogen varied from 18 to 53 mg. per hundred cubic centimeters, while the carbon dioxide and total proteins were quite normal. Tests of renal function gave essentially normal results, and there was no Bence Jones protein in the urine. Biopsy of sternal marrow revealed the marrow to be normal. A study of the calcium balance showed the total excretion of calcium over a three day period to be 1,500 mg., with an intake over this same period of 300 mg.

It was evident that this patient had hyperparathyroidism, and since at this time no extraneous cause could be found, her neck was explored and four perfectly normal parathyroid glands were visualized. Several weeks later she had a definitely palpable, although very small mass in the left breast, and at this time the left axillary lymph nodes were evident. Biopsy of these nodes revealed carcinoma secondary to the carcinoma of the breast.

Comment.—This patient, therefore, had secondary hyperparathyroidism, secondary to carcinoma of the breast with extensive metastasis to the bones. It should again be noted, as with the previous patient, that there were definite roentgenologic, chemical and metabolic changes of hyperparathyroidism in the absence of any gross changes in the parathyroid glands. It is interesting to observe the elevation of the blood phosphatase in this instance in contrast with the previous case. It is important to emphasize that the extensive bony changes present in these 2 cases were not due solely to the cancerous invasion of the bones but resulted in part from the hyperfunction of the parathyroid glands.

Cases of Hyperparathyroidism Secondary to Chronic Renal Disease

CASE 8.—L. U., a white woman aged 18, was admitted to the hospital for the first time in 1941. She had apparently been well up to six weeks before admission. At that time she noted swelling of the eyelids in the morning, some nocturia and no polyuria or hematuria. In addition, she noticed the appearance of many hard lumps under the skin of the legs. These lumps were painful on slight pressure. For three weeks prior to admission she had noticed night sweats and a low grade fever. The only significant point in her past history was an attack of scarlet fever at the age of 3 years.

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31. Rowntree, L. G.: Progress Relative to Diseases of the Ductless Glands, Pennsylvania M. J. **36**:646, 1933.

On examination her eyelids were found to be puffy. The ocular fundi were normal. The heart was not enlarged, and the blood pressure was 110 systolic and 50 diastolic. The radial arteries were thickened, and there was marked tortuosity of the left superficial temporal artery. There were many small, rounded, hard, tender subcutaneous plaques on both calves and around the ankles. On the skin of the axillas, the upper parts of the thighs and the buttocks there were innumerable pinhead-sized, firm, pinkish white papules. There was a considerable degree of anemia, the hemoglobin being 43 per cent and the red blood cell count 2,140,000. The blood urea nitrogen amounted to 120 mg. per hundred cubic centimeters, the blood calcium to 10.4 mg. and the phosphorus, determined on two occasions, to 8 and 10.5 mg. The total proteins amounted to 5.8 Gm. per hundred cubic centimeters, of which the albumin component was 3.2 and the globulin 3.6 mg. The carbon dioxide content was 35 volumes per cent; the chlorides amounted to 560 mg., the cholesterol to 180 mg. and the creatinine to 8.7 mg. per hundred cubic centimeters. The blood phosphatase was 21 King-Armstrong units. The urine showed fixation of specific gravity at 1.012 and contained small amounts of albumin and some white blood cells, red blood cells and an occasional hyaline cast.

The roentgenograms were particularly interesting: The skull showed generalized mottling. The arms, legs and abdomen showed numerous calcific deposits distributed extensively throughout the soft tissues. There were extensive calcifications of the vessels of the extremities and of the pelvis as well as of the splenic artery. All of the bones of the extremities showed diffuse osteoporosis. The ribs revealed similar osteoporotic changes as well as numerous small areas of rarefaction. The lumbar vertebrae also revealed a generalized osteoporotic process. Biopsy of one of the subcutaneous nodules revealed it to be calcium.

It was felt that this patient had chronic diffuse glomerular nephritis with secondary hyperparathyroidism. Following several transfusions, her general condition was improved, and she was discharged from the hospital one month after admission.

The patient was readmitted in October 1941, approximately two months after discharge. Her clinical condition had become decidedly worse. Many of the calcific nodules had ulcerated through the skin, producing painful sloughing areas. The blood urea nitrogen was 78 mg., the calcium 10.0 mg. and the phosphorus 9.7 mg. per hundred cubic centimeters. The carbon dioxide content was 31 volumes per cent.

It was obvious on admission that the patient was near death, and on the third day in the hospital she died.

On postmortem examination the four parathyroid glands were found to be unusually large and hyperplastic, the largest gland measuring 30 by 20 by 18 mm. There was extensive deposition of calcium throughout the soft tissues of the body but partciularly in the lungs and in the walls of the stomach. The kidneys showed the characteristic changes of chronic diffuse glomerular nephritis with marked contraction.

CASE 9.—K. K., a white woman aged 49, was admitted to the hospital in December 1941 because of marked weakness, anorexia, loss of 19 pounds (8.6 Kg.), polydypsia and polyuria of five months' duration. Thirteen years before admission she began to have pains across the back at the level of the upper lumbar vertebrae. This pain persisted for two years before the condition was adequately investigated. It was then discovered that she had chronic diffuse glomerular nephritis and that the blood pressure was 186 systolic and 110 diastolic. Her symptoms were fairly

stationary for nine years; then the pain in her back became more intense, and she noticed the onset of pains in other parts of her body, particularly in the knees. About five months prior to admission to the hospital she began to lose weight, suffered from anorexia and asthenia, and noticed increasing thirst and polyuria. Four months prior to her admission to the Mount Sinai Hospital she had been admitted to another hospital, where roentgen studies revealed a granular appearance of the skull, destructive changes in the acromion processes and a large cyst in the middle third of the left clavicle. The blood calcium amounted to 10.0 mg., urea nitrogen to 148 mg. and creatinine to 10.8 mg. per hundred cubic centimeters. No renal calculi were observed. The blood phosphatase was 23.4 Bodansky units. Biopsy of the cystic area in the left clavicle showed some scattered and some clumped multinuclear giant cells in a substratum of swollen connective tissue cells. In some places collagenization of what appeared to be miliary areas of hemorrhage were seen. At the periphery in some of the sections, small amounts of newly formed bone interspersed with connective tissue were observed. The pathologic diagnosis was "brown tumor" in a case of hyperparathyroidism.

Several weeks later the patient was admitted to the Mount Sinai Hospital wards. Roentgen examination of the skull showed a considerable increase in thickness of the cranium with obliteration of the diploe. There was coarse mottling throughout the calvarium. There was marked diffuse osteoporosis of the shoulder bones, and a large defect in the left clavicle was noted, as well as evidence of new bone formation around the periphery of this defect. There was diffuse osteoporosis of the long bones. There were mottling and thickening of the right pubis and ischium. The blood calcium varied from 11.1 to 12.4 mg. and the phosphorus from 8.1 to 6.3 mg. per hundred cubic centimeters. The urea nitrogen varied from 68 to 98 mg. per hundred cubic centimeters. The creatinine was 10.0 mg. per hundred cubic centimeters. The total protein, the total chloride and the cholesterol values were essentially normal. The phosphatase was 37 King-Armstrong units.

The patient was operated on, and four hyperplastic parathyroid glands were visualized, of which 2 were removed. Several weeks later the patient died in uremia. Permission for postmortem examination was not obtained.

Comment.—Cases 8 and 9 are typical instances of chronic renal disease with secondary hyperparathyroidism. The signs and symptoms of progressive renal failure antedated the onset of the bony changes and the results of chemical studies of the blood were typical of severe renal insufficiency. In both instances all four parathyroid glands were markedly hyperplastic.

SUMMARY

Nine cases of hyperparathyroidism are reported. In 5 of these cases the condition was primary, due to adenoma of a parathyroid gland, and in 4 it was secondary, due to chronic renal disease, multiple myeloma and carcinomatous metastasis to the bones. The pathologic physiology, the clinical considerations and the treatment are discussed.

SPONTANEOUS INTERSTITIAL EMPHYSEMA OF THE LUNG

WITH MEDIASTINAL, RETROPERITONEAL AND SUBCUTANEOUS EMPHYSEMA

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The occurrence of interstitial emphysema of the lung with air within the mediastinum as a result of thoracic trauma has been recognized for a long time. It has, of course, been described by many observers following medical and surgical maneuvers involving the lungs and pleura and associated with foreign bodies in the bronchial tree. The occurrence of mediastinal air and subcutaneous air has also been described as a complication of many pulmonary diseases, including tuberculosis, influenza, bronchopneumonia of various types and asthma. It has been known to occur when the intrabronchial pressures were elevated by the use of positive pressure anesthesia and during the efforts of labor. Hamman,[1] however, was the first to report the condition in healthy persons without antecedent trauma or disease. It was in 1934, in a paper discussing the diagnosis of coronary occlusion, that Hamman presented 2 cases of spontaneous mediastinal emphysema which simulated coronary occlusion. He added 4 cases in a paper in 1937 [2] and brought the total to 7 with a thorough discussion of the subject in 1939.[3] Since the recognition of the condition and the description of its clinical features by Hamman, other cases have been reported by Scott,[4] Morey and Sosman,[5] McGuire and Bean,[6] Kirshner,[7] Wolff,[8] Caldwell,[9] Matthews [10] and Pinckney.[11] Spontaneous mediastinal emphysema is apparently not uncommon in newborn infants, and the literature has recently been brought up to date by Gumbiner and Cutler.[12]

The clinical pictures encountered in all the cases of spontaneous interstitial emphysema of the lung thus far reported have been similar, and the condition is

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12. Gumbiner, B., and Cutler, M. M.: Spontaneous Pneumomediastinum in the Newborn, J. A. M. A. **117**:2050-2053 (Dec. 13) 1941.

largely dependent on the collection of air in the mediastinum. The onset is abrupt without any preceding illness or injury. The first symptom is pain of a severe type either in the side of the chest or substernally. When it begins in the side of the chest, it usually migrates to the substernal region or appears there after a pain-free interval. It may radiate to the neck or down the left arm and thus closely mimic the pain of coronary occlusion. The pain occasionally shows a slow steady increment in intensity; it is frequently markedly influenced by posture and often is accompanied by substernal tightness and a noise audible to the patient. A transient low grade fever has rarely been noted.

On examination of the patients, the pathognomonic sign described by Hamman is found. This is a peculiar crackling, crunching sound heard over the sternum and precordium which is synchronous with the heart beat. It may be heard with the patient in any position but frequently can be heard only with the patient in one position, such as lying on the left side. The area of impaired resonance to percussion normally present over the heart is in some instances replaced by hyperresonance. There may or may not be signs of pneumothorax, and a small amount of subcutaneous emphysema in the tissues of the neck or thorax is sometimes present. In a few instances rales have been described in isolated areas over the lung fields. The possibility of air traversing the aortic and esophageal openings in the diaphragm and appearing retroperitoneally has been mentioned but has not been described in any of the cases of spontaneous emphysema, although it is known to occur frequently in cases of emphysema due to thoracic trauma. Roentgenograms of the chest may or may not demonstrate the mediastinal air. A pneumothorax is occasionally shown. In 1 of the cases reported by Hamman there was minimal apical pulmonary tuberculosis, and in another case there was some increase in density at the base of the right lung which was interpreted as evidence of bronchiectasis. There have been no other roentgen signs of abnormality reported.

In all instances the process has been benign, complete recovery without sequelae occurring in several days. In a number of cases, however, there have been recurrences. Mediastinal compression sufficient to impede the circulation, which occurs not infrequently following trauma or in cases in which there is bronchial blockage due to foreign body, has not been present in these cases of spontaneous emphysema, although the possibility remains. No treatment has been required.

Considerable light has been thrown on the development of this condition through the experiments of Macklin,[13] largely with cats. By means of a ureteral catheter introduced into a bronchus, he has blown air into an isolated part of the lung, producing overdistention of the alveoli in this area. The alveolar ectasia thus produced actually causes the bases of the alveoli to pull away from the underlying blood vessels and gives rise to a pressure gradient from alveolus to vascular sheath favorable to the passage of air into the vascular sheath. The air then passes along the sheaths of the blood vessels to the mediastinum. Air may also dissect along strips of connective tissue and give rise to blebs on the pleural surface. In man it is probable that rupture of these blebs gives rise to the pneumothorax which often accompanies interstitial emphysema of the lungs. Kirshner [7] expressed the opinion that this is probably the most frequent mode of development of benign spontaneous pneumothorax. In his experimental animals Macklin has found that air escapes

13. Macklin, C. C.: Pneumothorax with Massive Collapse from Experimental Local Overinflation of the Lung Substance, Canad. M. A. J. **36**:414-420 (April) 1937; Transport of Air Along Sheaths of Pulmonic Blood Vessels from Alveoli to Mediastinum: Clinical Implications, Arch. Int. Med. **64**:913-926 (Nov.) 1939.

into the pleural space through rents in the mediastinal pleura, and this may also be the course in man. Air does not enter the mediastinal structures from a pneumothorax space, however, even in the face of high intrapleural pressures.

In experimental animals it is the insufflation of air which distends the alveoli and gives rise to the leakage of air. Macklin points out that atelectasis of an area of lung may likewise lead to overdistention of surrounding alveoli, with the same resultant pressure gradient from alveolus to vascular sheath and consequent perivascular emphysema. In support of this, Fisher and Macklin [14] reported a careful pathologic study of a child with foreign body atelectasis of the right lung and consequent distention of the left lung. They were able to demonstrate the alveolar ectasia in the left lung with the air in the vascular sheaths leading to mediastinal emphysema. Because it seems unlikely that perfectly normal alveoli in their normal

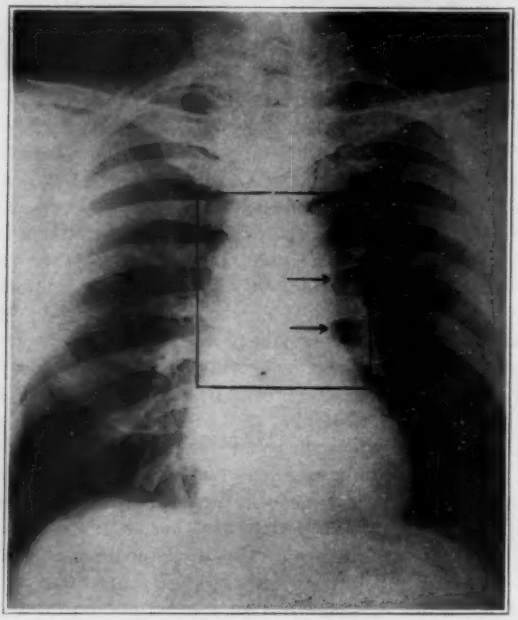

Fig. 1.—Posteroanterior roentgenogram of the chest taken Sept. 22, 1941. The arrows within the inset show the air distending the mediastinal pleura. At the base of the left lung the small dense area and the emphysema with paucity of lung markings above it can be seen. There is a calcified primary lesion of tuberculosis in this area.

anatomic relationships would allow the leakage of air, Macklin [15] has emphasized the need for a careful roentgen search for small atelectatic areas in persons with so-called spontaneous interstitial emphysema of the lung. The following case of interstitial emphysema of the lung has several interesting features.

14. Fisher, J. H., and Macklin, C. C.: Pulmonic Interstitial and Mediastinal Emphysema: Report of a Fatal Case in Which the Emphysema Occurred in a Child as a Result of the Aspiration of Peanut Fragments, Am. J. Dis. Child. **60**:102-115 (July) 1940.

15. Macklin, C. C.: Spontaneous Mediastinal Emphysema: A Review and Comment, M. Rec. **150**:5-7 (July 5) 1939.

REPORT OF A CASE

N. M., a white man aged 52, was admitted to the Pennsylvania Hospital on Sept. 1, 1941. He had been first seen in the neurologic clinic in January 1930, complaining of loss of strength and feeling in his left hand. He stated that he had had a penile lesion at the age of 22 and that he had received a few "shots for his blood" in 1926. Fixed pupils, absence of knee jerks and a definite ulnar palsy were noted, and a diagnosis of syphilis was made. The Wassermann reaction of the blood and of the spinal fluid was 4 plus, and the colloidal gold curve was of a dementia paralytica type. He received intermittent antisyphilitic therapy from that time until he was admitted to the hospital, on Sept. 1, 1941, specifically for fever therapy. The serologic reactions of his blood and spinal fluid had remained consistently positive. His only complaint on admission was a slight headache.

On examination he appeared well developed but somewhat poorly nourished. He was oriented, cooperative and presented none of the mental changes associated with dementia paralytica.

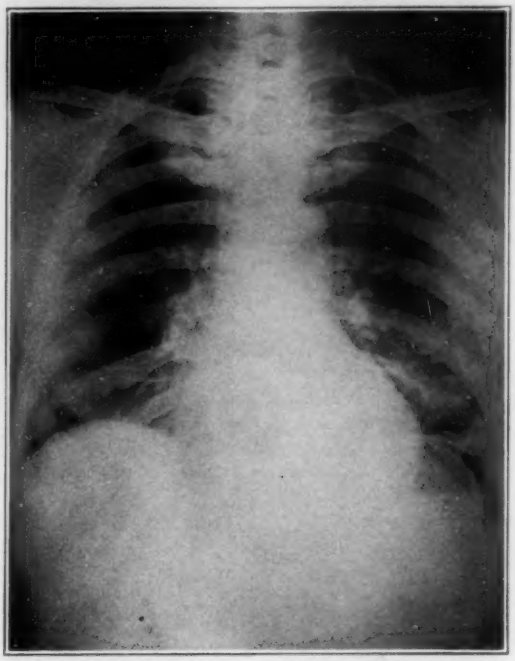

Fig. 2.—A roentgenogram taken during expiration on September 22 to rule out the existence of pneumothorax. The density at the base of the left lung can be seen to better advantage than in figure 1.

The temperature, pulse and respirations were normal, and the blood pressure was 110 systolic and 70 diastolic. The pupils were small and slightly irregular and failed to react to light. There were dental caries, and moderate pyorrhea, and the pharynx was slightly reddened. No abnormalities were noted in examination of the heart, lungs or abdomen. The knee jerks were absent; sensation was grossly normal. There were no abnormalities of sphincteric control. The urine was normal. The blood count showed 3,400,000 red blood cells and 7,500 white blood cells, with a normal differential count; there was 12 Gm. of hemoglobin per hundred cubic centimeters. The phenolsulfonphthalein excretion and the electrocardiogram were normal.

On September 10 fever treatments were started, each one consisting of approximately five hours' elevation of temperature to 105.6 F. in the Liebel-Flarsheim air-conditioned hypertherm. On the evening of September 19, after the fifth period of fever therapy, the patient noted a chilly sensation of short duration, and his temperature rose to 100.6 F. At the same

Fig. 3.—A roentgenogram of the abdomen taken September 23, showing the marked retroperitoneal emphysema outlining the kidneys.

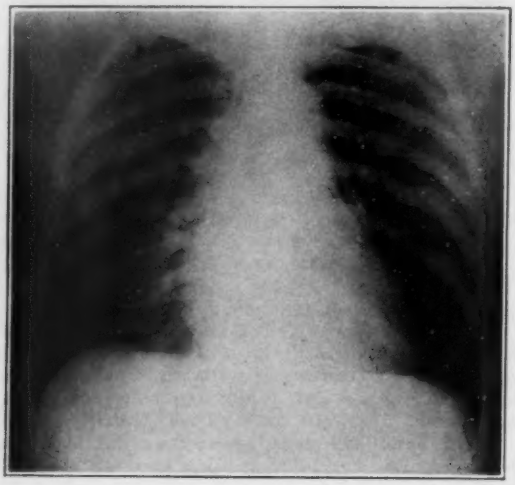

Fig. 4.—A posteroanterior roentgenogram of the chest taken September 29, showing the return to normal. The small density at the base of the left lung is now gone.

time he complained of scrotal swelling. This was not examined carefully and was interpreted first as angioneurotic edema. The following morning the temperature was normal, but widespread subcutaneous emphysema was present.

The patient first came under my observation on September 21, at which time his temperature, pulse, respirations and blood pressure were normal. He stated that he had had no pain at any time. On examination there was subcutaneous emphysema on both sides of the neck, on the left side of the thorax anteriorly, on the entire abdomen and in the region of the sacrum. The scrotum and penis were distended with air, and subcutaneous air extended down the left leg to the knee. Air could be felt in the tissues around the rectum by digital examination. The area of normal cardiac dulness was intact, but on auscultation over the sternum the crackling, crunching noises described by Hamman were clearly heard. They were synchronous with the heartbeat and could be heard throughout the cardiac cycle. They were independent of respiration and could be heard best with the patient in the recumbent position, although they were audible with him in any position. There was definite hyperresonance over the lower

Fig. 5.—A roentgenogram of the abdomen taken September 29, showing the small amount of residual air in the retroperitoneal spaces.

part of the left side of the chest posteriorly, and over this same area there were inspiratory crackling sounds which bore a striking resemblance to those sounds just described as occurring over the precordium. There was no subcutaneous emphysema over this area to confuse the findings. A roentgenogram taken the following morning (fig. 1) showed evidence of mediastinal air. There was a small density at the base of the left lung which was interpreted as an area of atelectasis. Just above this there was an area of greater penetration which suggested an area of lung containing a larger than normal amount of air. A small amount of subcutaneous emphysema could be seen in the neck. A roentgenogram was obtained during expiration (fig. 2) to make certain that a small pneumothorax was not overlooked, and none could be demonstrated. A roentgenogram of the abdomen showed a striking amount of retroperitioneal emphysema (fig. 3).

The signs rapidly disappeared, and by September 29, eight days later, nothing abnormal could be detected on examination of the patient. Another roentgenogram of the chest on that date (fig. 4) showed a return to normal with complete disappearance of the small area

of density at the base of the left lung and the area of emphysema above it. A roentgenogram of the abdomen (fig. 5) showed almost complete absorption of the retroperitoneal air. At this time the patient's vital capacity was 3,500 cc. Blowing against resistance failed to reproduce the abnormality. The fever treatments were reinstituted on October 1 and were continued to a total of twelve without any untoward reactions.

COMMENT

There are several points of interest illustrated by this case. In most of the cases thus far reported, pain has been a prominent feature and has focused the attention of the clinician on the mediastinum with the subsequent recognition of the pathologic process. The fact that large amounts of air can escape from the lungs and appear in the retroperitoneal and subcutaneous tissues without causing any pain may help to explain the origin of aberrant air in many puzzling situations. Two cases have recently been observed, one of terminal uremia and another of a pelvic abscess, in which there was unexplained subcutaneous emphysema of the abdominal wall. In neither case was there definite clinical evidence of air in the mediastinum, although it is highly probable that the subcutaneous air came from this source. The typical signs of mediastinal emphysema might conceivably be lacking if the air escaped readily from the posterior mediastinum and did not accumulate anteriorly.

The increase in mediastinal pressure is probably the factor which determines the production and severity of pain. It is therefore safe to assume that the ease with which air escapes the mediastinum is an important factor also. In this case there was apparently a safety valve from the mediastinum by way of the aortic and esophageal openings in the diaphragm. In this connection, it is interesting to recall the experiences of Torrey and Grosh [16] in an Army camp during the influenza epidemic of 1918. They found that in the cases in their locality there was considerable pulmonary and mediastinal emphysema among the afflicted persons. The patients had enlarged, hyperresonant chests with engorgement of the veins in the neck and suffered considerable pain. Those patients in whose necks large amounts of subcutaneous emphysema appeared showed striking and immediate improvement due to the release of mediastinal pressure.

It is also of interest that the site of alveolar leakage could be lateralized clinically. The hyperresonance and the peculiar crackling, crunching rales found at the base of the left lung and resembling those sounds heard over the mediastinum, were considered sufficient to determine this. The suggestive changes in the roentgenograms were considered to be confirmatory.

The finding of a small area of atelectasis in the roentgenogram is intriguing in the light of Macklin's suggestion that atelectasis leads to distention of surrounding alveoli with subsequent leaking of air into the vascular sheaths. There is an alternate hypothesis to explain this density, that is, that the surrounding emphysema could have compressed this small area represented by increased density in the roentgenogram. It seems most likely, however, that this density does represent an area of atelectasis.

The sounds heard over the mediastinum in this case were due entirely to air within the mediastinum. They were audible during systole and diastole and throughout the respiratory cycle. They were somewhat louder when the breath was held in the expiratory phase. These sounds differed entirely from the so-called

16. Torrey, R. C., and Grosh, L. C.: Acute Pulmonary Emphysema Observed During the Epidemic of Influenzal Pneumonia at Camp Hancock, Georgia, Am. J. M. Sc. **157**:170 (Feb.) 1919.

"pericardial knock" which has been described thoroughly by Lister [17] and that one hears at times during the course of therapeutic pneumothorax. Four cases have been observed during the last few years in which pericardial knock appeared for a time shortly after induction of therapeutic pneumothorax on the left side. In these cases the sound was a very loud, single, slapping sound, which was frequently palpable. Its intensity was greatest near the apex of the heart, and it was systolic. The sound was usually heard only with the patient lying on the left side and during one phase of the respiratory cycle. While the mechanism of production of this sound is not completely understood, it is felt that it was due to the pneumothorax and not to air within the mediastinum. A great deal of care must be exercised in differentiating pericardial knock from those sounds occurring as a result of air within the mediastinum. It is certainly true, however, that interstitial emphysema of the lung may lead to both mediastinal air and spontaneous pneumothorax in some cases.

No connection could be demonstrated between either the syphilis or the fever therapy used as treatment and the development of the emphysema in this case.

SUMMARY AND CONCLUSIONS

The literature regarding the clinical picture and pathogenesis of spontaneous interstitial emphysema of the lung has been reviewed.

Spontaneous interstitial emphysema of the lung with extension of air into the mediastinum commonly gives rise to subcutaneous emphysema in the neck. The air may also escape the mediastinum to the retroperitoneal spaces and produce subcutaneous emphysema in the lower part of the body. This may explain the presence of subcutaneous air in many otherwise puzzling situations.

A case of spontaneous interstitial emphysema of the lung with extension of air into the retroperitoneal and subcutaneous tissues is reported. The absence of pain in this case may have been due to the ease of escape of the air from the mediastinum, which prevented the development of high mediastinal pressures.

A small area of transient atelectasis was apparently responsible for the development of the interstitial emphysema of the lung in this instance. It was possible to locate clinically the site of escape of air from the alveoli into the perivascular and interstitial tissues of the lung.

It is felt that the auscultatory signs produced by air within the mediastinum differ in type and mode of production from the so-called "pericardial knock" sounds occasionally occurring in left-sided pneumothorax whether spontaneous or induced.

University Hospital.

17. Lister, W. A.: Pericardial Knock Associated with Spontaneous Pneumothorax, Lancet 2:1225 (Dec. 26) 1928.

BLUE SCLERAS, BRITTLE BONES AND DEAFNESS

A REPORT OF AN AFFLICTED FAMILY

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For centuries physicians have witnessed the tragic instance of a child born with multiple fractures of the bones. Lobstein,[1] in 1833, designated this condition as osteopsathyrosis, a descriptive term derived from Greek, meaning friable bones. In 1849, Vrolik reported a similar condition, which he named osteogenesis imperfecta, implying defective formation of bone as the cause. Spurway,[2] in 1896, reported the first instance in which the condition of fragile bones (fragilitas ossium) was associated with blue scleras. Bronson,[3] in 1917, and van der Hoeve and de Kleyn,[4] in 1918, added to the syndrome the third feature, deafness. Key,[5] in 1926, referred to the syndrome as "hereditary hypoplasia of the mesenchyme" and called attention to the hypotonicity of the ligaments with hypermobile joints. In 1928 Bell [6] collected 75 pedigrees including 489 cases of this abnormality. The condition is not so rare as is generally thought.

Recent literature [7] has shown renewed interest in the syndrome and indicates that there are essentially two schools of thought regarding the cause of the brittle bones, the one asserting that the disease is a developmental defect, the other, that it is a metabolic dysfunction. The first theory resulted from Key's study; the second followed the suggestion that the parathyroid glands [8] were responsible. Critics [9] of the latter theory have published data which suggest that the parathyroid glands are not implicated and that any association of dysfunction of these glands with the syndrome is fortuitous.

From the Edward J. Meyer Memorial Hospital and the University of Buffalo School of Medicine, Buffalo, and the Department of Pathology of the New York Post-Graduate Medical School and Hospital, Columbia University, New York.

1. Lobstein, J. G.: Traité d'anatomie pathologique, Paris, F. G. Lerrault, 1833, vol. 2, p. 204.

2. Spurway, J.: Hereditary Tendency to Fracture, Brit. M. J. **2**:844 (Sept. 26) 1896.

3. Bronson, E.: On Fragilitas Ossium and Its Association with Blue Sclerotics and Otosclerosis, Edinburgh M. J. **18**:240 (April) 1917.

4. van der Hoeve, J., and de Kleyn, A.: Blaue Sclera, Knochenbrüchigkeit und Schwerhörigkeit, Arch. f. Ophth. **95**:81 (Jan.) 1918.

5. Key, J. A.: Brittle Bones and Blue Sclera: Hereditary Hypoplasia of the Mesenchyme, Arch. Surg. **13**:523 (Oct.) 1926.

6. Bell, J.: Blue Sclerotics and Fragility of Bone, in Pearson, K.: Treasury of Human Inheritance, London, Cambridge University Press, 1928, vol. 2, pt. 3, sect. 24.

7. (*a*) Hills, R. G., and McLanahan, S.: Brittle Bones and Blue Sclerae in Five Generations, Arch. Int. Med. **59**:41 (Jan.) 1937. (*b*) Dessoff, J.: Blue Sclerotics, Fragile Bones and Deafness, Arch. Ophth. **12**:60 (July) 1934.

8. Takahashi, T.: Beitrag zur Kenntnis der blauen Sclera, Arch. f. Ophth. **115**:206, 1925. Dessoff.[7b]

9. Rados, A., and Rosenberg, L. C.: Relation Between Blue Scleras and Hyperparathyroidism, Arch. Ophth. **16**:8 (July) 1936.

The present communication concerns a family which has been affected with the Spurway syndrome through at least four generations, in which there has been no consanguinity. The family is of Scotch-English lineage. A genealogic tree has been outlined (fig. 1) accounting for 52 members. The data used to construct the genealogic tree were supplied by patients 7, 10 and 11; by patient 4, an uncle of patient 7, and by a cousin of patient 7, a physician (an unaffected member of the family). G. M., patient 7, knew all members of the family except patient 1; information about the latter was supplied by patient 4. The family is well aware of their abnormality. Twelve members of the family possess one or all of the features of the disease. One has only blue scleras. Seven have both blue scleras and brittle bones. Four have all three defects. Eight of the affected ones are males; 4 are females. Of 14 males exposed to the risk of inheriting the syndrome, 7 did inherit it. Of 10 females similarly exposed, 4 showed the syndrome. Thus,

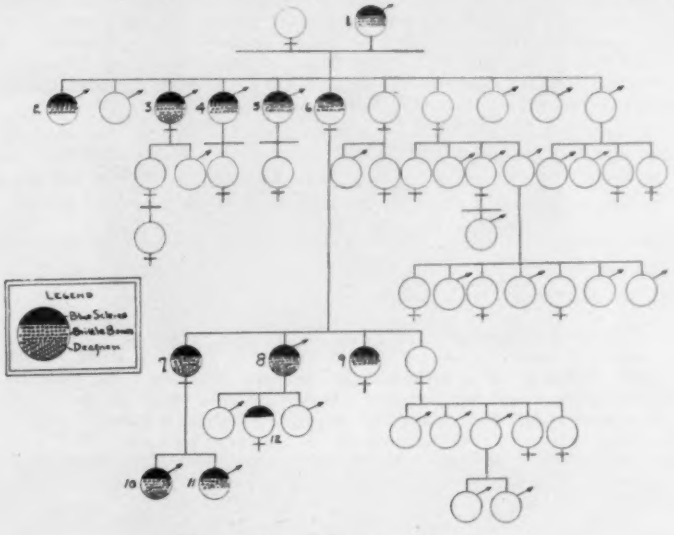

Fig. 1.—Genealogic tree of family.

of 24 children of seven matings heterozygous in respect to the phenotype under discussion, 11 inherited the anomaly. Transmission by a male parent occurred in 2 instances and by a female in 2 instances. Transmission took place directly between succeeding generations. The inherited factor thus appears to be a mendelian dominant and not sex linked.

CASE ABSTRACTS

The numbers used to designate patients in the following abstracts correspond to those on the genealogic tree.

1. D. C., an only son, had blue scleras and easily fractured bones. No information as to the number of fractures is available. He was slight, frail and of small stature. He died as a result of an abscess of the brain complicating acute mastoiditis. He was not known to be deaf. It is said that many of his relatives had blue scleras. His wife did not have the affliction. There is no information as to her family.

2. C. C., a son of D. C., had blue scleras and brittle bones. He died of pulmonary tuberculosis at the age of 27. No deafness had developed.

3. E. C., a son of D. C., is alive and well at the age of 65. He has blue scleras and brittle bones and is deaf. No information is available as to the exact number of fractures he has had, but there have been many.

4. G. C., a son of D. C., is alive and well at the age of 70. He has blue scleras and has had an unknown number of fractures but is not deaf.

5. W. C., a son of D. C., had blue scleras and brittle bones. He was apparently not deaf.

6. C. C. S., a daughter of D. C., had both blue scleras and brittle bones. There was at least one recognized dislocation, and she was small of stature. She died at the age of 74 years. There is good evidence that she was not deaf.

7. G. M., aged 50, a granddaughter of D. C., was interviewed and examined. She stated that she had sustained several fractures and numerous sprains in the course of her life, often caused by only slight trauma. She complained of having weak arches of the feet. During the past several years she had noticed progressive deafness. She related that she had a dietary idiosyncrasy, which is a family characteristic; i. e., she abstained from drinking milk. Physical examination revealed a healthy-appearing woman of 50 years. Her scleras were dark slate blue, and her hearing (watch test) was definitely impaired. She was small in stature (height 5 feet [152.5 cm.]) but well proportioned. All other physical findings were normal. Roentgenograms showed the various bones to be slender and definitely osteoporotic. Laboratory studies showed: blood calcium 10.7 mg. and blood inorganic phosphorus 3.7 mg. per hundred cubic centimeters; blood phosphatase 4.7 Bodansky units (corrected); total proteins 7.2 mg. per hundred cubic centimeters. Gastric analysis revealed normal acidity.

8. W. S., aged 42, alive and well, is a brother of G. M. He has blue scleras, is deaf and has suffered more than twenty fractures in the course of his life, most of these occurring in youth. He is described as being small of stature. Physical examination was not performed.

9. G. S. died in childhood. She had blue scleras and brittle bones but was not deaf.

Patients 10 and 11 were examined at the Mount Morris Tuberculosis Hospital, Mount Morris, N. Y. Dr. N. Stanley Lincoln, superintendent, gave us permission to publish the data concerning them.

10. G. O. M., a great grandson of D. C., was 25 years old at the time of examination. Since the age of 3 years he had had multiple fractures following slight trauma. On one occasion, while "chinning" on a horizontal bar, he broke an elbow. On another occasion he struck an arm against a wall and sustained a broken forearm. Most of his fractures occurred between the ages of 3 and 16 years, although recently he suffered a fracture of the left zygoma. There has been little or no displacement of the fracture segments. The location of the fractures were as follows: the left clavicle, a rib, the left zygoma, a phalanx (toe), the forearms, the elbows, the wrists, phalanges (fingers). Deafness and tinnitus were noticed for the first time at the age of 22 years and since have become progressively worse. He is able to hear low tones better than high tones. Since the onset of the deafness he has worn a hearing device. He, too, never drank milk and complains of having weak arches. He stated that his teeth erupted prematurely and that they decayed easily. Several extractions were necessary, and it was noted that the gums bled rather freely. The patient is frail and small of stature, and appears ten years older than his stated age. His height is 5 feet 4½ inches (164 cm.); his weight, 103 pounds (46.5 Kg.). His skull is large, but the facial features are small. His head has a relatively long anteroposterior diameter. The frontal and temporal areas are also rather prominent (fig. 2). Vision and the eyegrounds are normal. The scleras are china blue, the blue being most marked near the cornea and fading off slightly at the periphery. There is no evidence of keratoglobus. Otologic examination revealed a normal appearance of the drumheads. Tubal inflations gave no relief from the deafness. The Rinne test was negative; the Weber test showed hearing to be the same in both ears, and bone conduction is normal. The upper extremities show residual deformities from previous fractures. The humeri appear shortened. There is definite thickening about the elbow joints, with marked irregularity in the contour of both elbows. There is atrophy of the triceps muscles, particularly on the left. The forearms are small and free from deformity except in the immediate vicinity of the elbows. The finger tips are spatulous. The heart and the lungs were found normal. The blood pressure was 120 systolic and 80 diastolic. The remainder of the physical examination gave essentially negative results. Special studies included roentgen examination of all the bones, chemical analysis of the blood, gastric analysis and determination of the amount of calcium excreted in the urine and of the p_H of the stools. Roentgenograms of the patient's bones, compared with those of an apparently normal person, taken simultaneously, showed generalized increased radiability, which is interpreted as osteoporosis (fig. 3*A*). The skull

Fig. 2.—Profile view of patient 10.

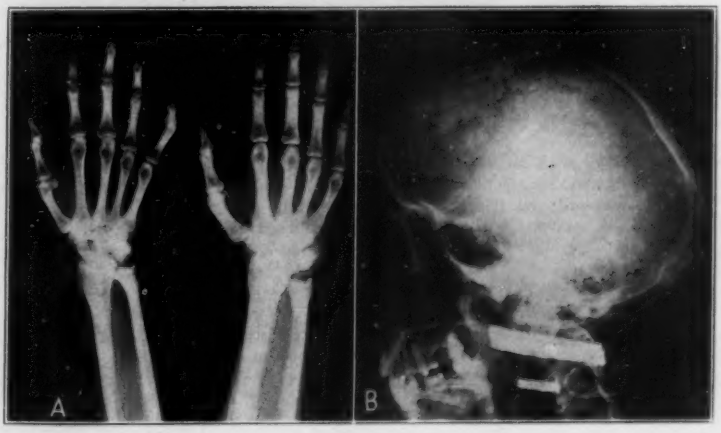

Fig. 3.—*A*, roentgenogram of a hand and forearm of patient 10 with that of a normal person for comparison, showing mild osteoporosis and old fracture of the little finger. *B*, roentgenogram of the skull of patient 10, lateral view, showing the increase in anteroposterior diameter and the prominent occiput.

showed an increase in both the anteroposterior and the bitemporal diameter. The occiput was unusually prominent (fig. 3 *B*). Chemical analysis of the blood gave results as follows: blood sugar 100 mg., nonprotein nitrogen 27 mg., urea nitrogen 11 mg., uric acid 3 mg., blood chlorides (as sodium chloride) 471 mg., calcium 9.9 mg., inorganic phosphorus 3.4 mg. and total proteins 8.1 mg. per hundred cubic centimeters; phosphatase activity 2.7 units (Bodansky). Gastric analysis following an alcohol test meal revealed the absence of free hydrochloric acid, a total acidity of 9 and a p_H of 6.3. A second test was then performed. The first sample was withdrawn after a test meal and the other samples at one-half hour intervals after injection of 0.5 cc. of histamine base (histamine acid phosphate). The usual effects of histamine, such as flushing of the face, throbbing sensations in the head, tachycardia and fall in blood pressure, were observed, but no free hydrochloric acid was secreted. The results are given in table 1.

The excretion of calcium in the urine was determined in two test periods while the patient was on a diet, the calculated (but not analyzed) composition of which was planned to provide a neutral ash, low calcium content.[10] The pertinent data are charted in tables 2 and 3. These

TABLE 1.—*Gastric Analysis After Stimulation with Histamine*

Sample	Total Acid	Free HCl	p_H	Blood	Microscopic Observations	Pepsin	Rennin	Mucus
1	5*	0	7.5	—	0	Slight	Slight	4+
2	15*	0	7.0	++	0	Slight	Slight	4+
3	25*	0	...	—	0	Normal	Normal	4+
4	35*	0	...	+	0	Normal	Normal	4+

TABLE 2.—*Urinary Calcium Excretion: First Test*

Day	Intake of Calcium, Gm. (Amount Calculated)	Excretion of Calcium, Gm. (Urine Analyzed)
1	0.21	.....
2	0.22	0.200
3	0.22	0.165
4	0.20	0.145

TABLE 3.—*Urinary Calcium Excretion: Second Test*

Day	Intake of Calcium, Gm. (Amount Calculated)	Excretion of Calcium, Gm. (Urine Analyzed)
1	0.13	.....
2	0.22	.....
3	0.17	.....
4	0.14	0.220
5	0.18	0.135

data showed an excretion of calcium in the urine somewhat in excess of the normal expectancy established by Aub and Farquharson[10] under similar controlled dietary restrictions. However, the excess is small and the period of observation short. It therefore appears highly improbable that there was any hyperparathyroidism, at least at this period of the patient's life.

The p_H of the stools, determined by a glass electrode on various occasions, varied between 7.2 and 5.6. The urine had a specific gravity of 1.015 and contained no albumin, sugar or abnormal cellular constituents. The Mosenthal test of renal function showed normal concentrating and diluting power, the specific gravity ranging from 1.005 to 1.021. The blood showed a hemoglobin content of 15.2 Gm.; the red cell count was 5,110,000; the white cell count was 10,500, with myelocytes 0 per cent, juvenile forms 0 per cent, stab forms 2 per cent, segmented forms 35 per cent, eosinophils 3 per cent, mononuclears 10 per cent and lymphocytes 50 per cent. The bleeding time was six minutes; the clotting time was seven and one-half minutes (capillary pipet). The basal metabolic rate was —8. Complement fixation tests for syphilis were negative.

11. W. M., aged 19 years, a son of G. M., was examined by us. He related a history (confirmed by his mother) of having been born with a dislocated hip and of having sustained

10. Aub, J. C., and Farquharson, R. F.: Studies of Calcium and Phosphorus Metabolism in Various Metabolic and Bone Diseases, J. Clin. Investigation **11**:235 (Jan.) 1932.

four fractures and repeated dislocations on slight trauma. He, too, has always refrained from drinking milk. Physical examination revealed a healthy young man with china blue scleras. He demonstrated "double jointedness" with marked hypotonicity of the ligaments. There was marked irregularity in the contour of each elbow, with thickening about the elbow joint, and a small portion of the left olecranon process was felt posterior to the lower end of the humerus and was freely movable. These were residues of fractures. There was no deafness. Roentgenograms showed that all the bones were slender and small in size, with varying degrees of osteoporosis. The olecranon process of the left ulna showed an old fracture with displacement upward and posteriorly to the articular surface of the humerus (fig. 4).

12. C. S., aged 6 years, a daughter of W. S., is alive and well. She has blue scleras but has not as yet shown any tendency toward fracture or dislocation of bones or toward sprains. Her hearing is unimpaired.

Fig. 4.—Roentgenogram of the elbow regions of patient 11, showing osteoporosis and deformity following fractures.

COMMENT

There is sufficient evidence that the syndrome under discussion is inherited. The present series conforms to the previously established dictum that unless blue scleras are present, the other features of the syndrome do not appear. Thus, the most constant feature of the syndrome is the scleral imperfection. The exact nature of this inherited anomaly is unknown. Whether a separate gene is concerned in the genesis of each feature of the syndrome is also unknown. Patients 7, 10 and 11 of the series have scleras varying from light blue to dark slate blue. The color was reputed to have varied similarly in those of their ancestors who had blue scleras.

It has been demonstrated that the majority of persons afflicted with the blue sclera syndrome are physically frail and small of stature. A characteristically shaped head has been frequently noted. In the affected persons whom Bronson [8] described there was unusual prominence of the frontal and occipital bones, one

group having the type of skull which characterizes patients with osteogenesis imperfecta. Patient 10 of the present series has prominent frontal and occipital areas of the skull. The head is disproportionately large. Patients 7 and 11 have heads of normal size and shape. However, these 3 members are small boned and except for patient 11 are small of stature. They have noted that those of their collaterals who have white scleras tend to be either of average height or taller than normal.

Deafness has developed in 4 of the affected members. Because several members of the family are yet quite young, deafness may still occur in them. The syndrome in patient 10 conformed almost entirely with Bezold's syndrome, which establishes a diagnosis of otosclerosis with ankylosis of the stapediovestibular joint. However, as previously noted, he was able to hear low notes by bone conduction, whereas in otosclerosis the reverse is true.

Seven of the members with blue scleras have bones that show a tendency to fracture easily. Several members complain more of sprains and dislocated bones than of fractures. A characteristic of patients 7, 10 and 11 is that they have weak arches. Patients 10 and 11 show a predilection for fractures about the elbow joints, where their principal deformities are seen.

The clinical and roentgenographic evidences of poor mineralization of the bones suggest excessive excretion of calcium, deficient absorption of calcific salts or idiosyncrasy of alimentation. Although 2 patients of the family under discussion habitually had dietary restrictions that might have been significant, it is quite unlikely that these dietary abnormalities occurred selectively in members of a family through four generations. One patient has gastric achlorhydria even after stimulation with histamine, and this, as is well known,[11] might lead to difficulties in the absorption of calcium from the intestines. However, we do not know whether this is merely an isolated individual aberration or a phenomenon occurring generally in persons with this syndrome. Several investigators [12] have reported cases in which the calcium balance was negative whereas others [13] found the calcium balance normal. Rados and Rosenberg [9] found normal excretion of calcium and phosphorus in the urine of their 2 patients. Since it seems well established that there is osteoporosis in this disease, the fact that there is lacking unequivocal chemical evidence of a negative chemical balance appears to us to be of lesser significance. Certainly a degree of calcium loss that could be determined with ease in necessarily short term metabolic studies would be incompatible with the longevity of life demonstrated in the afflicted members of this family. It is also conceivable that negative phases of calcium balance might occur only during certain restricted times in their lives, and it would be a matter of chance that these should be discovered. Certainly the tendency to fracture seems to be a recurring, cyclic affair, and diminishes with increase in age. This might conceivably be associated with endogenous changes, or it might be due to the varying exposure to risk of fractures at different times of life and the growing apprehension and personal solicitude that would come with maturity. Neither studies of phosphatase nor determinations of urinary calcium as done by others [9] and in the case of patient 10 warrant any

11. Zucker, T. F., and Matzner, M. J.: On the Pharmacological Action of the Antirachitic Active Principle of Cod Liver Oil, Proc. Soc. Exper. Biol. & Med. **21**:186, 1923-1924.

12. Hunter, D.: A Case of Osteogenesis Imperfecta, Lancet **1**:9 (Jan. 1) 1927. Tauber, M.: Beitrag zum Calciumstoffwechsel bei Osteogenesis imperfecta, Monatschr. f. Kinderh. **36**:12, 1927. Aub and Farquharson.[10]

13. Sindler, A.: Der Stoffwechsel bei Osteogenesis imperfecta, Ztschr. f. Kinderh. **42**:85, 1926. Stevenson, G. H., and Cuthbertson, D. P.: Blue Sclerotics and Associated Defects: Study of Four Families, with Notes on Their Mineral Metabolism, Lancet **2**:782 (Oct. 10) 1931.

attempt to implicate the parathyroid glands pathogenetically. There is fairly good histologic evidence [5] that patients with this syndrome have a defective osteoid matrix, particularly in intramembranous ossification. This is most likely genotypic in origin. Whether there is a second defect of calcium deposition metabolic in nature but likewise genotypic in origin is impossible to say. Further speculation with the limited data available is certainly fruitless.

SUMMARY

This study presents a previously unrecorded family of 52 members, 12 of whom have been affected with the blue sclera syndrome. Seven of the 12 members have both blue scleras and brittle bones. Four have these defects and deafness, and 1 has so far only blue scleras. Eight of the affected members are males; 4 are females. The condition is transmitted from generation to generation and occurs equally in both sexes. The physical attributes of small stature, hypermobility of the joints, relaxation of the ligaments and, often, abnormal shape of the head are found characteristically in involved members. Three members of the group have been studied in detail. Roentgenograms of the skeleton revealed slender bones, generalized osteoporosis and deformities resulting from multiple fractures. The present series conforms to the classic description of the syndrome as outlined by John Spurway (1896) and elaborated further by Bronson (1917), van der Hoeve and de Kleyn (1918) and Key (1926).

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NORMAL CARDIOVASCULAR ROENTGEN SILHOUETTE

STUDIED BY MEANS OF ROENTGENOGRAMS OF THE CHESTS OF CADAVERS AFTER OPAQUE SOLUTIONS HAD BEEN INJECTED INTO THE LARGE VESSELS AND CHAMBERS OF THE HEART

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For a proper interpretation of roentgenograms of the chest, an exact knowledge of the relations between the cardiac silhouette and the large vessels and chambers of the heart is necessary.

Many interesting studies of this subject have been made and published by Keith,[1] Dietlen, Roessler,[2] Parkinson[3] Vaquez and Bordet,[4] Delherm and Thoyer Rozat, and Laubry, Cottenot, Routier and Heim de Balsac,[5] but only the method followed by the last group has seemed to us quite convincing.

With a similar procedure, we have tried to determine clearly the relations that normally exist between the contour of the cardiac shadow in roentgen films and the different chambers and large vessels of the heart.

ROENTGENOGRAPHIC METHOD

In Juarez Hospital, of Mexico City, sodium iodide solution was injected into the large vessels and the chambers of the hearts of several cadavers. Roentgenograms were then taken of the chests of these cadavers placed in the dorsoventral position and in oblique positions.

Roentgenogram 1 was taken of a cadaver in the dorsoventral position after 70 cc. of a 50 per cent sodium iodide solution had been injected into the superior vena cava and the second and third costal cartilages resected. The distance between the tube and the film was 36 inches (91.5 cm.); the x-ray apparatus was generating radiant energy at 65 kilovolts and 80 milliamperes.

Roentgenogram 2 was taken of a cadaver in the dorsoventral position in the same way as roentgenogram 1 and after the same preparation plus an injection of 35 cc. of a 50 per cent sodium iodide solution into the ascending aorta.

Roentgenogram 3 was taken of the same cadaver as roentgenogram 2 with the chest in a 20 to 25 degree right anterior oblique position. The distance between the tube and the film was 36 inches, the time of exposure was one second and a half and the x-ray apparatus was generating radiant energy at 80 milliamperes and 70 kilovolts.

1. Keith, S.: Lancet **1**:1466 (June 27) 1936.

2. Roessler, H.: Clinical Roentgenology of the Cardiovascular System: Anatomy-Physiology-Pathology-Experiments and Clinical Application, Springfield, Ill., Charles C Thomas, Publisher, 1937; Atlas of Cardioroentgenology, ibid., 1940. Golden, R.: Diagnostic Roentgenology, New York, Thomas Nelson & Sons, 1937.

3. Parkinson, J.: Lancet **1**:1337 (June 13); 1391 (June 20) 1936.

4. Vaquez, H., and Bordet, E.: Radiologie du coeur et des vaisseaux de la base, Paris, Masson & Cie, 1928.

5. Laubry, C.; Cottenot, P.; Routier, D., and Heim de Balsac, R.: J. de radiol. et d'électrol. **19**:193 (May); 561 (Oct.) 1935; Presse méd. **102**:2071 (Dec. 21) 1935; Radiologie clinique du coeur et des gros vaisseaux, Paris, Masson & Cie, 1939.

Roentgenogram 4 was taken of the same cadaver placed in a left anterior oblique position. Roentgenogram 5 was taken of a cadaver in the dorsoventral position after injection of 35 cc. of a 50 per cent sodium iodide solution and resection of the second and seventh costal cartilages.

Other roentgenograms were taken, but they either were not clear enough for a correct interpretation or did not afford us more information than was furnished by the five sent with this paper.

Fig. 1.—Vessels and right chambers of the heart of a cadaver in the dorsoventral position. The roentgenogram was taken after injection of 70 cc. of sodium iodide solution into the superior vena cava and resection of the second and third costal cartilages.

STUDY OF THE ROENTGENOGRAMS

1. *Vessels and Right Chambers of the Heart in the Dorsoventral Position (fig. 1).*—The right innominate vein (more than 50 mm. long and 10 mm. wide) is nearly vertical, forming an angle of 10 degrees with the vertical axis. The left innominate vein is only partially opaque. Its direction is nearer to the horizontal, with which it forms an angle of 40 degrees.

On the upper part of the right side of the normal cardiac shadow one perceives a short, nearly vertical segment placed above the so-called right superior arch. It is obvious from this roentgenogram that this segment corresponds to the right innominate vein, placed behind the innominate artery.

Both innominate veins join to form the superior vena cava (80 mm. long and 16 to 20 mm. wide in this roentgenogram), which forms the right side of the contour of the cardiac shadow in that place called by some authors the superior right arch.

At the junction of the two upper thirds and the lower third of the so-called right superior arch is the hilar shadow as found on the normal roentgenogram of the chest. This is placed lower in the right lung than in the left. The site of this shadow is occupied in this roentgenogram by the ascending and descending branches of the right division of the pulmonary artery. The angle of division of these arteries is just 110 degrees.

One can see in this roentgenogram that the inferior right arch is formed by the right atrium and that the short straight segment placed below is the supradiaphragmatic portion of the inferior vena cava as stated by Laubry, and that it is not formed by the hepatic veins as stated by Roessler. In the cadavers which we have dissected, the hepatic veins join the inferior vena cava below the diaphragm. In this roentgenogram, as well as in others we have taken, the hepatic veins join the inferior vena cava below the diaphragm.

The right ventricle is only partially filled on account of the valvular and papillary structures. The pulmonary artery, its right and left divisions and the ascending and descending branches of these were well filled with the opaque solution.

One can see in this roentgenogram that the middle arch in the left side of the cardiac silhouette is formed mainly by the pulmonary artery and by its left division. This fact must be emphasized.

One can see also that the right division of the pulmonary artery is longer than the left and that the left pulmonary hilus is higher than the right.

In this roentgenogram the pulmonary artery is 26 mm. long and 21 mm. wide; the right branch is 60 mm. long and 25 mm. wide. The apparent length of the left branch is 24 mm. and the apparent width is 24 mm.

The cardiac shadow is in contact with the hepatic shadow for a distance of 70 mm. and with the gastric clearness for a distance of 25 mm. The portion of the cardiac shadow in contact with the hepatic shadow is formed by the right ventricle for 50 mm. and by the right atrium for 20 mm. The angle of division of the left pulmonary artery is 150 degrees and is placed on the upper part of the middle left arch, a little outward from the contour of the cardiac shadow. This is the place normally occupied by the left pulmonary hilar shadow.

2. *Vessels, Right Chambers of the Heart and Aorta in Dorsoventral Position (fig. 2).*—The shadow obtained is quite similar to the former but the aorta is filled with the opaque solution. This filling is not complete in the ascending aorta.

One can clearly see that the ascending aorta is normally placed to the left of the superior vena cava and that normally the superior right arch of the cardiac silhouette is formed by the superior vena cava and not by the ascending aorta.

The left primitive carotid artery was filled with the opaque solution, showing that the intrathoracic portion of this artery is very long (60 mm.). One can appreciate how difficult it would be to reach the aorta by palpation on the suprasternal depression as some clinicians in our country pretend to do.

One can see that the superior left arch is formed by the aorta and that the straight segment placed above this arch is formed by the left carotid and the left subclavian artery.

3. *Vessels, Right Chambers of the Heart and Aorta in Right Anterior Oblique Position (fig. 3).*—One can easily recognize the superior vena cava and the ascending aorta. The width of the former is 20 mm. and that of the latter is 28 mm. One can recognize too, on account of the oblique direction of the vessel, a small portion of the descending aorta.

Fig. 2.—Vessels, right chambers of the heart and aorta of a cadaver in the dorsoventral position, taken under the same conditions as roentgenogram 1 except that an additional 35 cc. of the opaque solution had been injected into the ascending aorta.

The contour of the shadow of the heart and large vessels in the right oblique position is formed on the spinal side by the superior vena cava in the upper part

and by the right atrium in the lower part. On the other side the contour is formed from the cranial end downward by the pulmonary artery and its left division and by the left ventricle.

4. *Vessels, Right Chambers of the Heart and Aorta in Left Oblique Anterior Position (fig. 4).*—The contour of the roentgen shadow in this position is formed

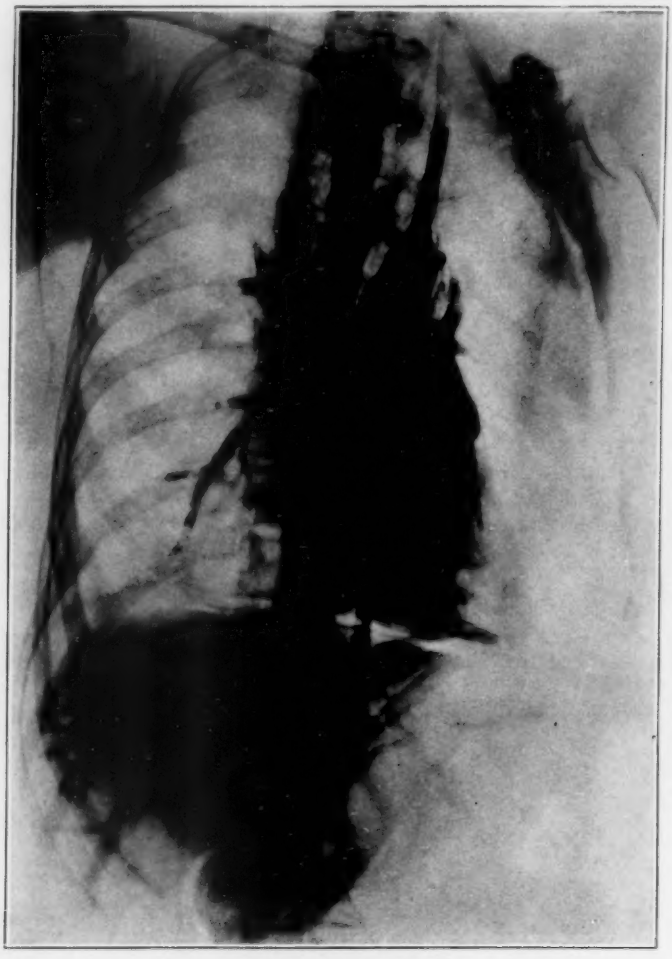

Fig. 3.—Vessels, right chambers of the heart and aorta in the cadaver shown in figure 2, taken with the chest in a right anterior oblique position.

on the ventral side by the superior vena cava in the upper part, by the ascending aorta in the middle portion and by the right ventricle in the lower part. On the dorsal side this contour is formed from the cranial end downward by the ascending aorta in the upper part, by the pulmonary artery in the middle portion and by the left antrum in the lower portion.

One can appreciate that the aorta, though in this roentgenogram visible in its three portions (ascending, transverse and descending), is normally visible only in its ascending portion, the transverse portion being superimposed on the tracheal clearness and the descending aorta on the shadow of the vertebrae.

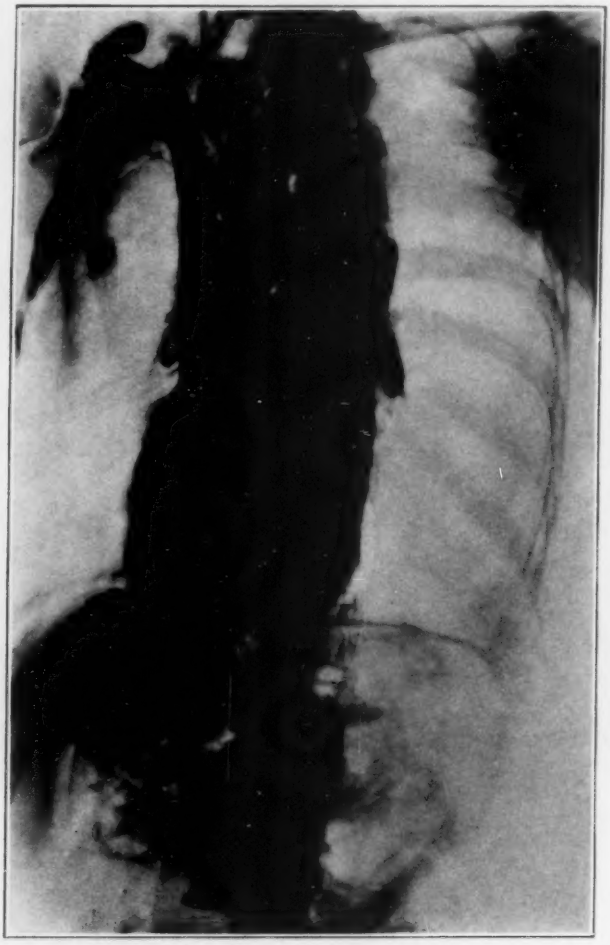

Fig. 4.—Vessels, right chambers of the heart and aorta in the cadaver shown in figures 2 and 3, taken with the chest in a left anterior oblique position.

5. *Pulmonary Veins, Left Chambers of the Heart and Aorta in Dorsoventral Position (fig. 5).*—The left antrum is normally placed behind the left ventricle. Consequently, only a small portion of it is visible in roentgenograms taken in the dorsoventral position, forming then the lower portion of the middle left arch.

Pulmonary veins are visible in the pulmonary field. They reach the right side of the cardiac silhouette on the upper part of the right inferior arch, below the pulmonary hilar shadow. They reach the left side of the contour of the cardiac

shadow on the lower part of the left middle arch, a little below the left pulmonary hilar shadow.

One can thoroughly appreciate how great is the distance between the aortic arch and the sternal fourchet (38 mm. in this roentgenogram). The apparent length of the ascending aorta is 55 mm.; its diameter, 21 mm.

Fig. 5.—Pulmonary veins, left chambers of the heart and aorta of a cadaver in the dorso-ventral position after injection of 35 cc. of the opaque solution and resection of the second to seventh costal cartilages.

COMMENT

In our roentgenograms some interesting facts become apparent that have not been enough emphasized in medical literature.

The normal shadow of the pulmonary hilus in roentgenograms has the same place and the same form as the shadow of the right or the left division of the pulmonary artery at the site of its branching into an ascending and a descending artery. The place of the left pulmonary hilar shadow is the upper part of the left

middle arch and that of the right is the lower part of the right superior arch; they are just the places of the branching of the left and right divisions of the pulmonary artery. The sites of the pulmonary veins are lower and correspond to the lower portion of the middle arch on the left and to the upper part of the inferior arch on the right.

The shadow of the pulmonary hilus in thoracic roentgenograms of normal subjects is therefore mainly *vascular* and even *arterial* in nature.

In roentgen kymograms taken with this field in view, one of us (Dr. Meneses Hoyos) and Dr. Gómez del Campo have always recognized the pulsation of the normal shadow of the pulmonary hilus, as shown in figure 6.

The middle arch on the left side of the cardiac shadow is formed mainly by the pulmonary artery *and its left division.*

The upper portion of the shadow located in the middle of the chest is formed neither by the aorta nor by the superior vena cava but by the innominate veins,

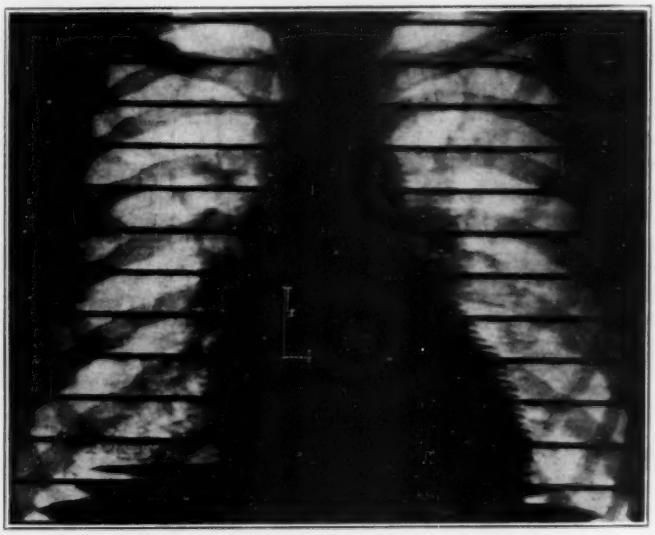

Fig. 6.—Roentgen kymogram showing pulsation in the shadow of the pulmonary hilus (Dr. C. Gómez del Campo).

the innominate artery, the left carotid artery and the left subclavian artery. The short straight segment placed above the superior right arch is formed by the innominate vein covering the innominate artery. The short straight segment placed above the superior left arch is formed by the superposition of the left carotid and left subclavian arteries.

The distance between the aorta and the sternal fourchet varies widely in roentgenograms of normal persons but is always several centimeters, and the aorta is not to be easily reached by palpation of the suprasternal depression.

SUMMARY AND CONCLUSIONS

The right side of the cardiac silhouette is formed from the cranial end downward by a short, nearly vertical segment corresponding to the innominate vessels, by the so-called right superior arch, which normally corresponds to the superior vena

cava, placed normally to the right of the ascending aorta, and by the inferior right arch, corresponding to the right atrium. The very short straight segment sometimes visible in the lower part of this silhouette is formed by the inferior vena cava. The suprahepatic veins were totally subdiaphragmatic in the cadavers we studied.

The left side of the cardiac silhouette is formed from the cranial end downward by a straight segment corresponding to the left carotid and left subclavian arteries, by the middle arch, corresponding on its upper portion to the *left division of the pulmonary artery,* on its middle portion to the pulmonary artery and on its lower portion to the left atrium, and by the inferior left arch, corresponding to the left ventricle.

In our roentgenograms the lower and outward pole of the shadow of the heart, usually called the apex, corresponds entirely to the left ventricle.

The shadows normally obtained at the sites of the pulmonary hili correspond to the branching of the right and the left division of the pulmonary artery. They are mainly *vascular* and even *arterial* in nature.

The silhouette of the heart and vessels in a right anterior oblique position is formed on the spinal side by the superior vena cava on its upper portion and by the right atrium on its lower portion. This same silhouette is formed on the ventral side from the cranial end downward by the ascending aorta (the innominate vessels and the left carotid and subclavian arteries being nearly transparent to roentgen rays), the pulmonary artery and its left division, and the left ventricle.

The silhouette of the heart and large vessels in roentgenograms taken in a left anterior oblique position is formed on the ventral side by the superior vena cava on the upper portion, by the ascending aorta on the middle portion and by the right ventricle on the lower portion. On the spinal side it is formed on the upper part by the aorta, on the middle portion by the pulmonary artery and on the lower portion by the left atrium.

Normally, only the ascending portion of the aorta is visible on a roentgenogram taken in a left anterior oblique position, the transverse portion being superimposed on the tracheal clearness and the descending portion on the shadow of the vertebrae.

Lisboa 32.

SERUM CONCENTRATION AND RENAL CLEARANCE OF POTASSIUM IN SEVERE RENAL INSUFFICIENCY IN MAN

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The fact that during each day a normal person ingests by mouth and excretes in the urine and stool several grams of potassium had led to use of the expression "potassium balance." Since approximately 80 per cent of the output of potassium is excreted by the kidney, it has usually been assumed that the renal parenchyma possesses a special ability to excrete this ion. Indeed, the rapid renal excretion of potassium after the ingestion of a considerable amount of a potassium salt has been suggested as a reason for the nontoxic effect of potassium on the normal organism. If renal excretion is seriously impaired, as it may be in the presence of renal disease, it might be suspected that retention of potassium in the blood serum analogous to retention of other excretory constituents of the urine would occur. In animals with experimentally produced lesions of the kidneys, including bilateral nephrectomy, bilateral ligation of the ureters, bilateral chronic roentgen ray nephritis and intoxication with uranium and mercury bichloride, a progressive increase in the potassium concentration of the serum has been observed and has been regarded as a retention phenomenon.[1] Among human beings who have severe renal insufficiency, however, the values for serum potassium have not been found to be consistently increased. Among patients who have similar high degrees of retention of urea, the concentration of potassium in the serum may be increased in some and normal or even subnormal in others.[2] This rather considerable variation

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1. (*a*) Noguchi, I.: Untersuchungen über den Mineralstoffwechsel in Nierenkranken, Arch. f. exper. Path. u. Pharmakol. **108**:73-77, 1925. (*b*) Beckmann, K.; Bass, E.; Dürr, R., and Drosihn, G.: Stoffwechsel und Blutveränderungen nach Nierenextirpation. Ionenvirschiebungen und Säure-Blasengleichgewicht nach Nierenexstirpation, Ztschr. f. d. ges. exper. Med. **51**:333-341, 1926. (*c*) Mark, R. E., and Kohl-Egger, E.: Kalium-Kalziumspiegel im Serum nach Harnstoffgabe, Zentralbl. f. inn. Med. **48**:578-584 (June) 1927. (*d*) Hartwich, A., and Hessel, G.: Der Kalium-, Calcium- und Kochsalzspiegel bei den verschiedenen Formen der experimentellerzeugten Urämie, Klin. Wchnschr. **7**:67-69 (Jan. 8) 1928. (*e*) Nicholson W. M., and Schechter, A. J.: Cardiac Arrhythmia After Bilateral Ureteral Ligation in the Dog, Bull. Johns Hopkins Hosp. **60**:346-357, 1937. (*f*) Bolliger, A., and Breh, F.: Ueber die Mineralstoffveränderungen des Blutes bei experimenteller Nephritis, mit spezieller Berücksichtigung des Kalium-Kalziumspiegels im Serum, Zentralbl. f. inn. Med. **49**:825-831 (Sept.) 1928.

2. (*a*) Meyers, V. C., and Short, J. J.: The Potassium Content of Normal and Some Pathological Human Bloods, J. Biol. Chem. **48**:83-92 (Sept.) 1921. (*b*) Zondek, H.; Petow, H., and Siebert, W.: Zur Frage der Funktionsstörung der Niere, Klin. Wchnschr. **1**:2172-2174 (Oct. 28) 1922. (*c*) Wilkins, L., and Kramer, B.: Studies on the Potassium Content of Human Serum, Arch. Int. Med. **31**:916-922 (June) 1923. (*d*) Briggs, A. P.: A Study of the Inorganic Elements of Blood Plasma, J. Biol. Chem. **57**:351-357 (Sept.) 1923.

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in values for serum potassium among such patients seems to indicate that the concentration of serum potassium may be altered not only by impaired renal function but also by extrarenal factors. Of the latter the most obvious would be changes in the complicated ionic balances in the body fluids and tissue cells. To obtain additional information regarding this problem it seemed advisable, while a group of these patients were being observed in the hospital, to estimate repeatedly the concentration of potassium and certain other constituents in their blood serum and also to determine the volume of serum cleared of potassium by their urine during a given period. The following report is the result of clinical and chemical investigations of 33 patients who had definite renal insufficiency. Pathologic study also was carried out on 14 of them.

SELECTION OF PATIENTS

The 33 patients included in this study were of two groups: (1) patients with chronic diffuse nephritis and (2) patients with subacute nephritis and passive congestion (table 1). The first group was comprised of 29 patients who were selected because they were suffering from chronic disease of the kidneys and definite renal dysfunction. The primary diagnosis for 8

TABLE 1.—*Distribution by Condition: Thirty-Three Cases of Definite Renal Insufficiency*

Condition Present	Cases	
	Total Number	Numerical Designation
Chronic Diffuse Nephritis		
Chronic nephrosclerosis *	8	1 through 8
Chronic pyelonephritis	2	9 and 10
Chronic glomerulonephritis (no potassium salt given)	16	11 through 26
Chronic glomerulonephritis (potassium salt given)	3	27 through 29
Total	29	1 through 29
Subacute Nephritis and Passive Congestion		
Indeterminate subacute process	1	30
Subacute bilateral thrombosis	1	31
Passive congestion †	2	32 and 33
Total	4	30 through 33

* In case 6 potassium chloride was injected once intravenously.
† In case 32, 15 Gm. of potassium nitrate was given by mouth.

of these patients was chronic diffuse arteriolar disease with marked involvement of the kidneys, or chronic nephrosclerosis; for 19, chronic glomerulonephritis, and for 2, chronic pyelonephritis. Renal insufficiency was extreme in 26 of these patients; the severity of renal dysfunction was indicated by greatly increased concentrations of urea and creatinine in the blood. The remaining 3 patients, who had chronic glomerulonephritis (cases 27, 28 and 29 in table 1), were included because to each of them a potassium salt was administered. They did not have such severe renal insufficiency as did the other 26 patients, and in 2 of them (cases 28 and 29) features of chronic lipid nephrosis were present.

In the second group of 4 patients (cases 30 through 33 in table 1), rapid progressive renal insufficiency developed while the patients were under observation. The cause in 1 of them was obscure; in the second arterial thrombosis with multiple infarcts of both kidneys occurred, and in the remaining 2 there was marked congestion of the kidneys secondary to myocardial failure.

(*e*) Nelken, L., and Steinitz, H.: Ueber den Gehalt des Blutserums an Calcium und Kalium bei Nierenkrankheiten, Ztschr. f. klin. Med. **103**:317-341, 1926. (*f*) Salvesen, H. A.: Variations in the Serumelectrolytes in Diseases of Renal Origin with Special Reference to the Cause of Renal Acidosis, Acta med. Scandinav. **69**:126-186, 1928. (*g*) Green, C. H.; Wakefield, E. G.; Power, M. H., and Keith, N. M.: The Electrolyte Distribution and the Acid-Base Equilibrium in the Serum in Cases of Nephritis and Nephritic Acidosis, Biochem. J. **26**:1377-1382, 1932. (*h*) Hoffman, W. S., and Jacobs, H. R. D.: The Partition of Potassium Between the Serum and Corpuscles in Health and Disease, J. Lab. & Clin. Med. **19**:633-644 (March) 1934. (*i*) Atchley, D. W.; Loeb, R. F.; Benedict, E. M., and Palmer, W. W.: Physical and Chemical Studies of Human Blood Serum: II. Study of Twenty-Nine Cases of Nephritis, Arch. Int. Med. **31**:611-615 (April) 1923.

TABLE 2.—*Clinical and Pathologic Observations* [a]

Case	Age, Yr.	Sex	Edema, Grade 0 to 4	Hemoglobin, Gm. per 100 Cc.	Erythrocytes, Millions per Cu. Mm.	Blood Pressure, Mm. Hg	Ocular Fundi	Died *	Diagnosis
4	42	M	0	8.0	2.90	190-240 110-170	Retinitis	D	Clinical: diffuse arteriolar disease with hypertension group 3; myocardial degeneration with early failure Necropsy: Diffuse arteriolar disease (hypertension) with superimposed glomerulitis
7	38	M	0-2	11.6 9.1	4.1 3.4	180-260 120-180	Retinitis; papilledema	D	Clinical: diffuse arteriolar disease with hypertension group 4; myocardial degeneration and decompensation; acute pericarditis; edema of brain Necropsy: arteriolar sclerotic atrophy of kidneys; fibrinous pericarditis
11	16	M	0-3	5.8 7.6	2.51 3.16	125-160 90-130	Retinitis	—	Clinical: chronic glomerulonephritis; pulmonary congestion
14	25	F	0	5.3	1.50	175-245 125-160	Retinitis; papilledema; disks anemic	D	Clinical: chronic glomerulonephritis; diffuse arteriolar disease with hypertension group 4 Necropsy: chronic glomerulonephritis
15	21	M	1-2	4.3	1.40	150-185 100-130	Acute angiospastic retinitis; anemia and edema of disks	D	Clinical: chronic glomerulonephritis; pericarditis Necropsy: chronic glomerulonephritis; fibrinous pericarditis; chronic tuberculosis of lungs and hilus nodes
18	21	M	0-1	6.6	3.00	180-220 110-160	Retinitis; papilledema	D	Clinical: chronic glomerulonephritis; diffuse arteriolar disease with hypertension group 4; myocardial degeneration and decompensation; pulmonary edema; bronchopneumonia Necropsy: granular atrophy of kidneys; hypertrophy of heart; bronchopneumonia
19	31	M	0	9.6	3.60	100-220 65-130	No retinitis	—†	Clinical: chronic glomerulonephritis Necropsy: advanced chronic glomerulonephritis with renal atrophy
24	64	F	0-1	6.2	2.95	140-230 70-105	No retinitis; no hemorrhages	—	Clinical: chronic glomerulonephritis; chronic pyelonephritis (?); diffuse arteriolar disease with hypertension group 2; uremia
25	37	M	0	5.5	2.2	140-190 90-140	Anemia; no retinitis	D	Clinical: chronic glomerulonephritis; severe anemia; myocardial degeneration with decompensation Necropsy: chronic glomerulonephritis; uremia; fibrinous pericarditis
26	23	M	0-1	10.0 7.0	3.7 2.5	120-160 80-100	Anemia; no retinitis	D	Clinical: chronic glomerulonephritis
27	16	F	0	6.3	2.10	140-180 95-125	Retinitis; anemia	—	Clinical: chronic glomerulonephritis
30	25	M	0-1	12.3	3.87	120-170 70-100	Essentially normal	D	Clinical: acute renal insufficiency (etiology ? unknown toxic medication ?); diabetes mellitus Necropsy: Hypertrophy of kidneys (combined weight 627 Gm.); hydropic degeneration of tubules and glomeruli; extensive subacute central necrosis of liver

* Died in the hospital while under observation.
† Died at home thirty-two days after dismissal.

OBSERVATIONS

Clinical and Pathologic Observations.—A summary of the significant clinical data obtained in 12 of the series of 33 cases and the pertinent pathologic observations in 8 of them are given in table 2.[3] Seventeen patients were men and 16 were

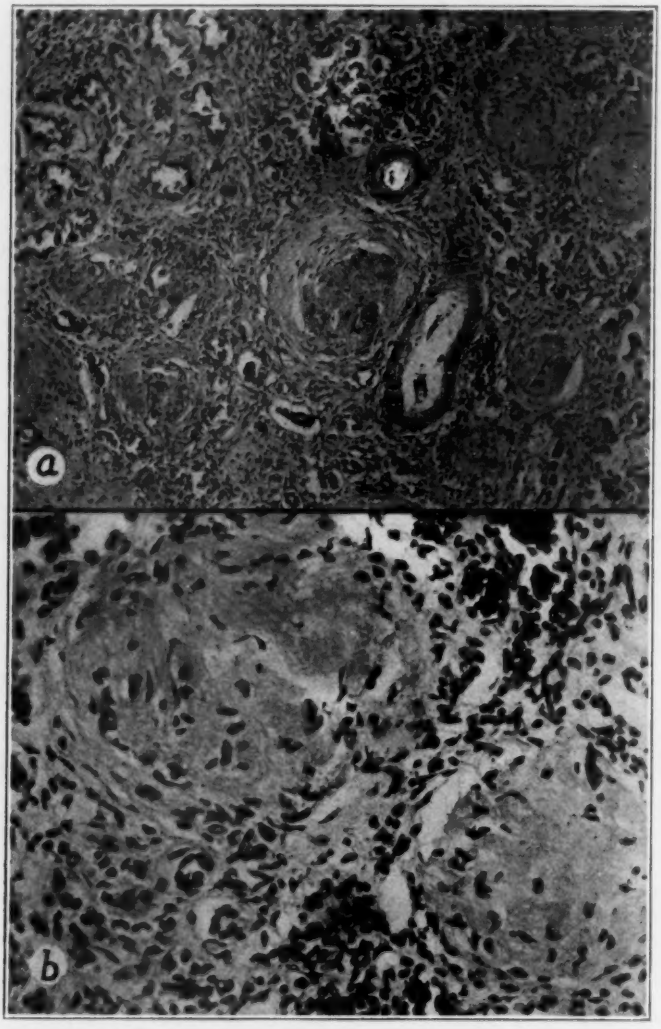

Fig. 1 (case 14).—Sections from a kidney (hematoxylin and eosin; *a*, × 100; *b*, × 320). There are numerous hyalinized glomeruli and atrophy of the tubules. An increase in interstitial connective tissue and collections of lymphocytes can be seen. The vessels appear to be fairly normal, but in other sections (not shown) of this kidney pronounced arteriolosclerosis with almost complete obliteration of the lumens could be seen. Arteriosclerosis also was marked.

3. Observations in all 33 cases were extremely valuable, but for purposes of conservation of space the data for only 12 appear in extenso in tables 2 and 3.

women, and their ages varied from 16 to 64. Moderate to severe anemia usually was present. Observations made in case 15 (table 2) revealed the most severe anemia, the concentration of hemoglobin decreasing to 4.3 Gm. per hundred cubic centimeters and the erythrocyte count to 1,400,000 per cubic millimeter. Definite hypertension was present in 28 patients and absent in 2, whereas in the 3 remaining

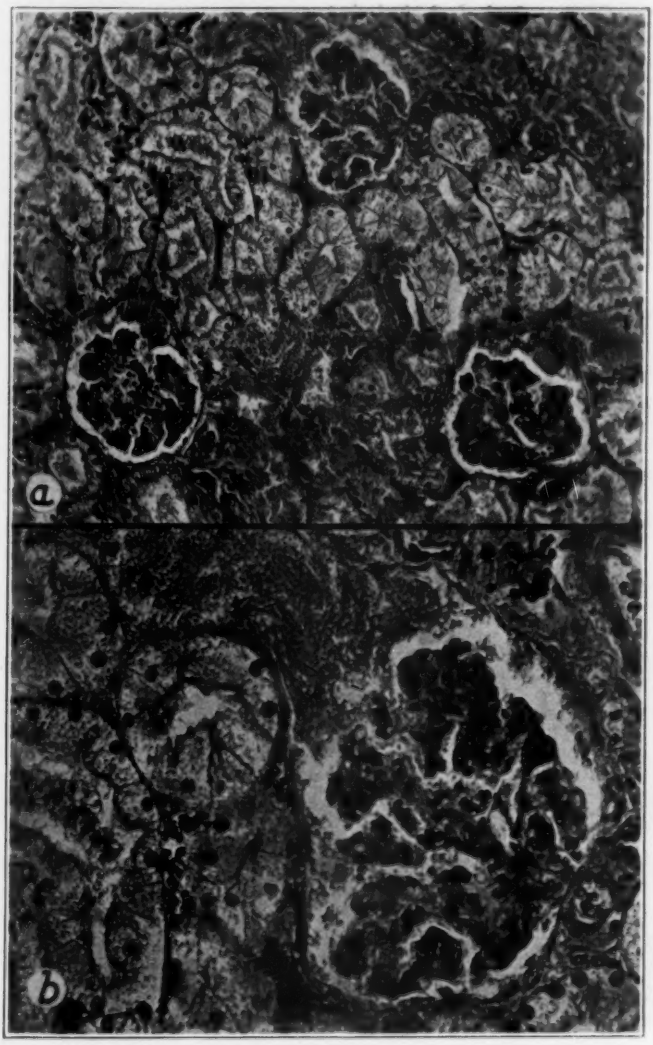

Fig. 2 (case 30).—Sections from a kidney (hematoxylin and eosin; *a*, × 125; *b*, × 300). There is hydropic degeneration of the tubules, the cells having a pale, foamy, edematous appearance. Many tubules contain casts of albuminous material and some contain pus. In occasional tubules there is calcium material with more advanced degenerative changes. Glomeruli and arterioles appear to be fairly normal.

patients the blood pressure usually was normal but on a few occasions increased to abnormal values.

The course of the illness after examination in this series of patients emphasizes the serious nature of the renal lesions. Seventeen patients died while they were under observation in the hospital, and 15 died later, but within eight months of their dismissal. A single patient (case 29) is alive thirty-two months after dismissal. This patient had renal dysfunction which was much less severe than that of any other in the series, and the data are included because potassium salts had been administered for their diuretic action. Therefore conditions during the treat-

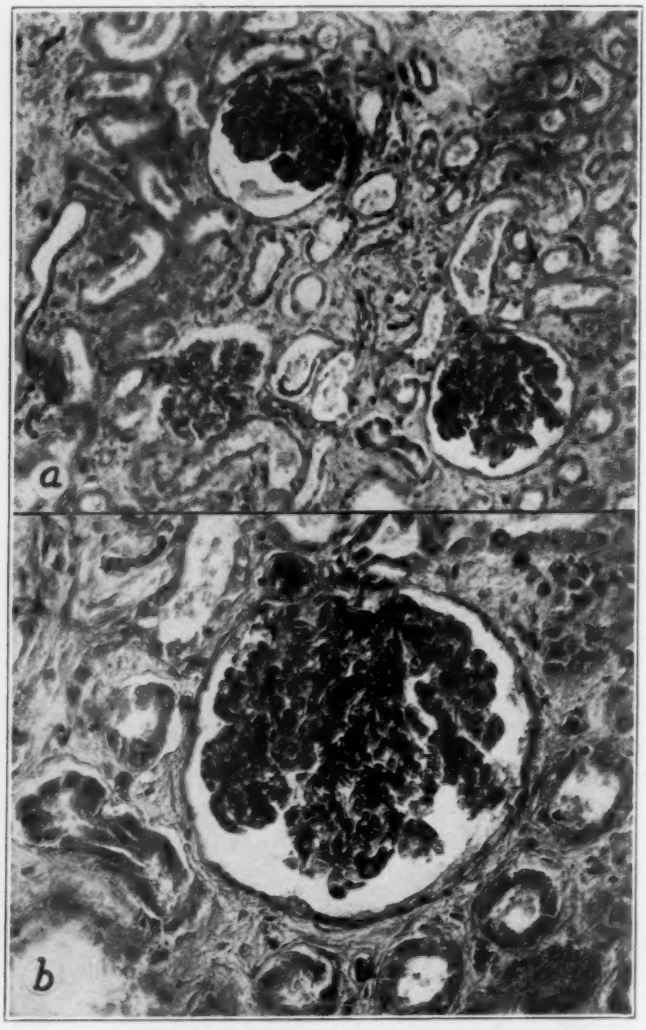

Fig. 3 (case 32).—Sections from a kidney (hematoxylin and eosin; *a*, × 125; *b*, × 300). Marked congestion and occasional focal atrophy of tubules (chronic infarction). Evidence of severe passive congestion. Old pyelonephritic scar. Little foci of atrophy of tubules, with fibrosis and interstitial lymphocytes. Glomeruli congested, but glomerulitis not present. Deposits of calcium and casts in tubules. No arteriolar sclerosis of any degree.

ment of this patient afforded a good opportunity for study of the effects of the ingestion of potassium salts on renal function and on the concentration of potassium in the serum.

TABLE 3.—*Chemical Studies of the Blood*[3]

		Blood			Serum							Plasma		
		Hg., Gm. per 100 Cc.	Mg. per 100 Cc.		Gm. per 100 Cc.		Mg. per 100 Cc.					Potassium	Mg. per 100 Cc.		CO_2 Combining Power, Vol. %
Case	Hospital Day		Urea	Creatinine	Protein	Albumin	Potassium	Sodium	Calcium	Phosphorus	Sulfate	Sodium Ratio	Chlorides (as Chlorine)	Cholesterol	
4	5	8.0	188	11.2	5.8	4.1	19.2	308	...	...	15.3	0.0624	327	...	47.5
	14	...	274	16.0	...	...	25.8	310	...	...	22.8*	0.0830	351	228	47.5*
	18†														
7	1	...	116	5.4	...	...	.....	...	...	...	15.7	.....	...	...	57.9
	20	11.6	420*	10.4*	...	...	22.2	325	...	...	.....	0.0683	340*	...	33.4*
	23	...	396*	10.4*	...	...	25.4	...	8.5	...	.....	.....	...	...	.....
	35	...	306	8.8	...	...	25.0	...	...	...	22.9*	.....	353*	...	39.0*
	45	9.1	356	6.4	6.0	3.5	23.9	...	...	...	.....	.....	...	185	.....
	58†														
11	3	5.8	286	16.8	6.1	3.6	19.6	307	...	9.6	.....	0.0638	327	...	24.0
	7	...	346	.....	5.9	3.5	22.2	284	4.3	...	.....	0.0784	264	...	27.0
	9	...	346	16.0	5.7	3.1	19.5	296	4.6	14.7	.....	0.0659	276	...	27.0
	14	...	272	13.6	...	...	21.0	319	4.6	...	.....	0.0658	270	...	72.0
	17	...	267	14.6	...	...	18.7	313	4.3	9.9	.....	0.0597	313	...	61.0
	25	...	266	13.6	...	...	22.2	313	3.9	8.8	.....	0.0700	...	...	.....
14	3	5.3	214	12.0	5.3	...	17.6	...	...	...	20.5	.....	349	...	32.8
	4	...	...	.....	...	...	18.2	305	6.3	...	.....	0.0597	330	...	.....
	7†														
15	2	4.3	220	13.2	4.9	1.9	.....	...	...	...	20.8	.....	373	...	27.6
	4	...	266*	15.2*	...	...	27.8	...	...	...	.....	.....	...	181	.....
	8	...	392	18.4	...	...	40.9	290	...	...	.....	0.1410	...	...	.....
	9†														
18	1	6.6	332	16.0	5.9	4.3	20.7	290	...	...	41.0	0.0714	280	...	46.6
	2	...	...	.....	...	...	22.3	...	...	...	49.0	.....	...	...	.....
	3†	...	396	18.4	...	...	34.2	296	...	...	50.4	0.1157	...	...	44.9
19	19	9.6	358*	18.4*	...	...	20.3	308	...	...	30.7*	0.0659	317*	...	35.3*
	20	...	356	.....	...	...	17.8	...	...	...	.....	.....	...	...	.....
24	3	6.2	90	4.4	...	...	.....	...	...	...	.....	.....	...	...	.....
	6	...	81	...	...	...	30.1	...	...	...	12.7	.....	...	...	.....
	10	...	90	4.2	...	...	31.2	...	...	...	10.8	.....	...	...	.....
	13	...	110	5.7	...	...	35.1	296	...	...	.....	0.1185	343	...	52.0
	15	...	130	4.5	...	...	38.8	...	...	5.2	13.5	.....	...	...	.....
	16	...	138	...	...	...	34.6	...	8.3	...	.....	.....	...	...	.....
25	3	...	276	20.0	...	...	.....	...	...	...	24.2	.....	314	...	32.2
	6	...	252	18.4	...	...	20.9	...	...	...	.....	.....	...	...	.....
	13	5.5	258	18.4	...	...	27.7	...	...	...	.....	.....	309	...	50.4
	16‡	...	...	.....	5.7	...	34.2	...	...	...	.....	.....	...	175	.....
	20	...	326	22.4	...	...	31.0	305	...	...	.....	0.1016	...	...	39.0
	28	...	424	20.0	5.4	3.5	33.5	...	...	17.3	.....	.....	...	...	27.7
	30†														
26	2	10.0	94	...	4.3	2.1	.....	...	...	...	9.9	.....	...	...	.....
	8	...	...	...	...	...	34.1	...	...	...	.....	.....	388	277	35.3
	14	...	154	3.4	...	...	32.7	...	...	...	.....	.....	...	...	.....
	28	...	248	3.8	3.3	...	31.0	288	6.8	8.8	.....	0.1076	338	...	29.6
	40	...	327	5.2	...	...	25.7	...	...	...	.....	.....	316	...	32.4
	50	...	394	7.6	...	...	27.4	273	...	...	.....	0.1004	306	370	36.2
	55†														
27§	4	6.3	124	7.6	5.1	3.4	32.9	...	...	...	.....	.....	...	...	.....
	6	...	...	...	...	...	31.0	...	...	...	.....	.....	...	...	.....
	7	...	118	8.4	5.3	3.5	37.3	...	...	...	.....	.....	413	...	38.0
30	2	12.3	258	10.0	...	...	.....	...	...	...	.....	.....	...	...	49.4
	5	...	288	15.2	4.9	3.5	19.7	296	...	...	38.6	0.0666	317	273	34.3
	6†														

* These values were not obtained on the same specimen of blood as the corresponding values of potassium, but were for other specimens obtained within forty-eight hours.

† Day of death.

‡ On the sixteenth day the patient received 300 cc. of citrated blood by transfusion. The concentration of potassium in blood serum immediately after transfusion was 34.1 mg. per hundred cubic centimeters as compared with 34.2 mg. in specimen withdrawn prior to transfusion.

§ This patient ingested a potassium salt during observation in the hospital. Details of the amount taken are given in table 4.

Pathologic studies[4] in 10 cases of the group in which the condition present clinically appeared to be chronic renal disease revealed diffuse chronic lesions

4. Dr. A. H. Baggenstoss, of the section on pathologic anatomy of the Mayo Clinic, made the pathologic observations.

throughout the kidneys (fig. 1, case 14). On the other hand, in the group of 4 cases in which rapid progressive renal insufficiency developed necropsy revealed subacute renal lesions in 2 (fig. 2, case 30) and severe congestion in 2 (fig. 3, case 32). The adrenal glands were examined in 13 cases in which necropsy was performed, because of the known relationship between the hormones of the adrenal cortex and potassium metabolism. Histologic study did not reveal any distinctly abnormal condition; in a few of the cases of diffuse arteriolar disease the walls of some of the arterioles of the capsule and of the gland itself were distinctly thickened. Rabinowitch [5] in 1925 suggested a possible relationship between a high potassium: sodium ratio in the blood serum and dilatation of the heart. In 5 of his patients with a high potassium: sodium ratio in the serum he observed pronounced dilatation of the heart at necropsy. Our experience in 3 cases was somewhat different (tables 1, 2 and 3). In case 9, with the concentration of potassium in the serum increased

TABLE 4.—*Effect of Potassium Salts on the Concentration of Potassium in the Blood Serum of Five Patients*

Case	Hospital Day	How Given	Amount, Gm.	Period of Administration, Days *	Serum Potassium, Mg. per 100 Cc.	Blood Urea, Mg. per 100 Cc.	Diagnosis
6	17	.....	.....	..	18.9	336	Chronic nephrosclerosis
	18	Intravenously	7.2 KCl in 900 cc. solution				
	20	.....	.....	..	22.4	368	
27	6	.....	.....	..	31.0	...	Chronic glomerulonephritis
	7	Per os	5.0 $KHCO_3$	..	37.3	118	
28	111	.....	.....	..	22.6	...	Chronic glomerulonephritis
	122	Per os	46 KNO_3	11	33.1	114	
	152	Per os	66 KNO_3	30	23.1	76	
29	4	.....	.....	..	24.4	...	Chronic glomerulonephritis
	9	Per os	40 KNO_3	5	24.7		
	14	Per os	27 KNO_3 10 KCl	5	26.8		
	19	Per os	21 KNO_3 12 KCl	5	27.7	60	
	26	Per os	76 KNO_3	7	25.0	52	
32	5	Per os	15 KNO_3	3	....	...	Passive congestion of kidney
	9	.....	.....	..	34.2	196	

* Period of administration completed on the evening of the previous day.

to 34 mg. per hundred cubic centimeters and the potassium: sodium ratio to 0.1062, there was no evidence of cardiac dilatation. However, in cases 15 and 18 both the concentration of potassium in the serum and the potassium: sodium ratio were distinctly increased and moderate dilatation of the left ventricle was observed at necropsy.

Observations in Chemical Studies of the Blood.—Results of chemical studies of the blood [6] of certain of our 33 patients are listed in tables 3 and 4. It is apparent that severe renal insufficiency and retention of certain metabolites in the blood were the rule. The abnormally high retention of metabolites in 29 patients is strikingly shown by the mean concentration of urea, creatinine and sulfate in the

5. Rabinowitch, I. M.: On the Relative Proportions of Sodium, Potassium, Calcium and Magnesium in Blood Plasma in Renal Disease, J. Biol. Chem. **62**:667-673 (Jan.) 1925.

6. The blood obtained from patients in this study was withdrawn from a vein in the elbow, in the morning, before the ingestion of food.

blood. These mean concentrations were 242, 12.2 and 27.2 mg. per hundred cubic centimeters respectively. Some degree of acidosis was present in 30 of 33 patients, as indicated by a reduction in the carbon dioxide–combining power of the plasma. This reduction varied considerably; it was slight in some patients and extreme in others. Hypochloremia was present in many patients, and the concentration of sodium in the serum also was often considerably reduced. Our finding that the concentration of both the chloride in the plasma and the sodium in the serum was frequently reduced in cases of severe renal insufficiency is in agreement with previous experience.

The concentration of phosphorus in the serum was determined for 10 patients and was found to be increased in all; the actual values were 5.0 to 17.3 mg. per hundred cubic centimeters. The content of calcium in the serum was estimated for 13 patients; it varied from 3.9 to 10.2 mg. per hundred cubic centimeters. Symptoms of tetany were not present, even in patients who had very low concentrations of calcium in the serum. There was, however, no correlation found between increases of phosphorus or decreases of calcium and the increment of potassium in our series of patients. The cholesterol content of the plasma was definitely increased to more than 300 mg. per hundred cubic centimeters in 5 patients (cases 8, 17, 26, 28 and 29), and in all 5 edema and hypoproteinemia also were present.

Analysis of our data with regard to the concentration of potassium in the blood serum reveals some very interesting observations. The concentration varied from 12.8 to 40.9 mg. per hundred cubic centimeters, as compared with a normal range of 17 to 21.3 mg.[7] Such an increased variation over normal seems difficult to explain. However, on further examination it is evident that patients with persistent severe renal insufficiency who have a subnormal or normal value for serum potassium on a single occasion will later often, although not invariably, be found to have an abnormally high concentration of potassium. Actual results show that for 14 of the 33 patients a single value was within the normal range, whereas on the other hand 24 of the 33 patients had at least one value which was more than the maximal normal, 21.3 mg. per hundred cubic centimeters. In 16, or 66 per cent, of the latter 24 patients the serum potassium reached a concentration of more than 25 mg. These results give ample evidence that in the presence of uremia, repeated determinations of the concentration of potassium in the serum often will reveal an abnormal increase, whereas a single estimation may not.[8]

In cases 24, 26 and 27 interesting results are disclosed: the initial concentrations of potassium in the serum were abnormally high, 30.1, 33.7 and 32.9 mg. per hundred cubic centimeters, although the urea and creatinine in the blood had not increased to extremely high levels, the values for urea being 81, 154 and 124 mg. and those for creatinine 4.4, 3.4 and 7.6 mg. respectively (table 3). Several investigators have previously noted a high value for potassium in the serum of a single

7. This was the range obtained in a series of normal persons by Furey (Furey, E. D.: Normal Variations in Proteins and Certain Inorganic Elements of the Blood Serum, Proc. Staff Meet., Mayo Clin. **13**:730-732 [Nov. 16] 1938).

8. In diabetes mellitus (Rathery, F., and Bertoliatti, J.: Variations du taux du potassium dans le sang et diabète sucré, Compt. rend. Soc. de biol. **116**:1346-1349, 1934. McQuarrie, I.; Thompson, W. H., and Anderson, J. A.: Effects of Excessive Ingestion of Sodium and Potassium Salts on Carbohydrate Metabolism and Blood Pressure in Diabetic Children, J. Nutrition **11**:77-101 [Jan.] 1936), in tetany,[2c] in wound shock,[2a] in certain allergic states (Rusk, H. A.; Weichselbaum, T. E., and Somogyi, M., with the technical assistance of Simms, E.: Changes in Serum Potassium in Certain Allergic States, J. A. M. A. **112**:2395-2398 [June 10] 1939. Hoffman and Jacobs [2b]), in burns and in some infections accompanied by fever increases in serum potassium to more than normal have been reported. In the present series of cases we believe these conditions have been excluded with the exception of fever.

similar patient. In our 3 patients (cases 24, 26 and 27) the serum potassium was sustained at a high level, although the patients continued to excrete a considerable volume of urine. As renal insufficiency increased in case 26 from the fourteenth to the fortieth day in the hospital, there was a gradual decrease in the concentration of potassium in the serum from 33.7 to 25.7 mg. (fig. 4, case 26).

The results in cases 4, 15, 18 and 25, in which chronic nephritis was present, emphasize that terminal renal failure, with oliguria in cases 15 and 18 but with a considerable output of urine in case 4, may be accompanied by an increase in serum potassium (fig. 5, case 25). Bolliger and Breh [11] reported similar results in chronic experimental nephritis produced by roentgen rays. In case 15, during terminal renal failure, when acute pericarditis developed and the concentration of serum

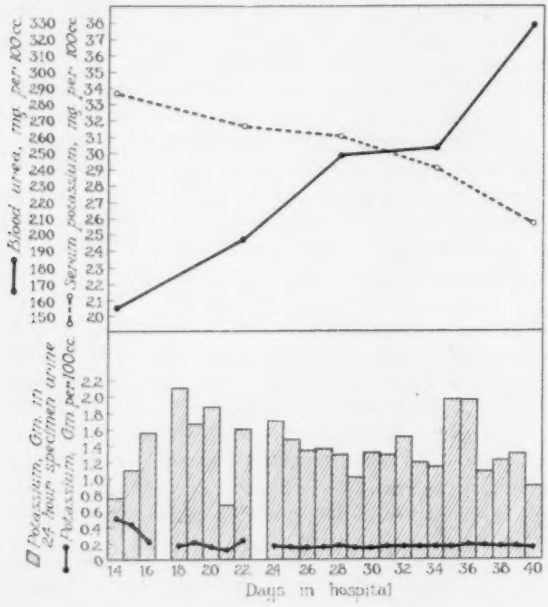
Blood urea, mg. per 100 cc.
Serum potassium, mg. per 100 cc.
Potassium, Gm. in 24 hour specimen of urine
Potassium, Gm. per 100 cc.
Days in hospital

Fig. 4 (case 26).—Contrast between the concentration of urea in the whole blood and the concentration of potassium in the serum. On the fourteenth day, with an increase in urea to 154 mg. (three times normal), the value for potassium was relatively high (33.7 mg.) As the content of urea steadily increased to reach 327 mg. on the fortieth day, the content of potassium decreased, to 25.7 mg. Early in this period the concentration of potassium in the urine gradually decreased and then remained at a fixed value; the total output of potassium in the urine remained fairly constant throughout the entire period of twenty-six days. Note that on the twenty-second day the concentration of potassium in the serum was 31.7 mg. and the concentration in the urine was 207 mg., six times greater than that in the serum.

potassium was increasing rapidly, electrocardiograms were made on several occasions. These tracings revealed some very definite progressive changes, which were similar to those reported by Hoff, Smith and Winkler [10] in experimentally produced

9. Footnote deleted on proof.

10. Hoff, H. E.; Smith, P. K., and Winkler, A. W.: The Cause of Death in Experimental Anuria, J. Clin. Investigation **20**:607-624 (Nov.) 1941.

intoxication with potassium (fig. 6, case 15).[11] These investigators expressed the beliefs that the abnormal results seen in electrocardiograms obtained in their experiments were caused by the increase in the concentration of potassium in the serum and that death of an animal in the presence of such experimentally produced intoxication is due to cardiac failure, which in turn is brought about by the high concentration of potassium in the serum. We cannot entirely exclude the possibility that the early electrocardiographic changes noted in case 15 might be due to acute pericarditis which was present at this time, but we think the evidence is strongly suggestive that the later changes were due to potassium intoxication. If these changes in the electrocardiogram developed as a result of the high concentration of potassium in the circulating plasma, 40.9 mg. per hundred cubic centimeters, or 10.4 milliequivalents, we believe these tracings are the first to indicate the occurrence of such intoxication in a patient suffering from chronic nephritis and uremia. In this connection Cushny [12] made a very interesting statement in 1917, when he said that a concentration of potassium in blood plasma "in anything over about 50 mg. per cent is highly poisonous to the heart." The evidence in case 15 that potas-

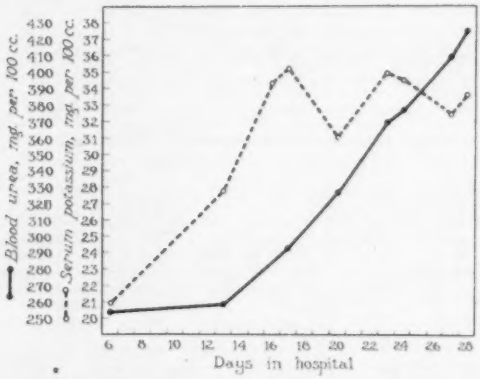

Fig. 5 (case 25).—Contrast between the concentration of urea in the whole blood and of potassium in the serum of a patient with terminal uremia. On the sixth hospital day the value for urea was 252 mg. (five times normal) and that for potassium was 20.9 mg., a normal figure. From that day until death there was a distinct increase in the concentrations of both urea and potassium.

sium might be playing a causative role in the production of the toxemia in uremia revives a viewpoint hinted at by Meissner [13] in 1866, suggested by Voit [14] in 1868 and discussed at length by Feltz and Ritter [15] in 1881.

11. In case 32 the electrocardiogram showed on the seventh hospital day an intraventricular conduction defect with a QRS complex of 0.16 second. On the patient's first day in the hospital the QRS complex was of normal duration, and it seems possible that the change might be attributed to an increase in the concentration of potassium in the serum, as has been suggested in case 15 (table 4). Further support to this suggestion was the absence of any demonstrable myocardial lesions on histologic examination. Dr. H. B. Burchell interpreted these electrocardiographic tracings.

12. Cushny, A. R.: The Secretion of Urine, London, Longmans, Green & Co., 1917.

13. Meissner, G.: Bericht über Versuche die Urämie betreffend, Ztschr. f. rat. Med. **26**:225-249, 1866.

14. Voit, C.: Ueber das Verhalten des Kreatins, Kreatinins und Harnstoffs im Thierkörper, Ztschr. f. Biol. **4**:77-162, 1868.

15. Feltz, V., and Ritter, E.: De l'urémie expérimentale, Paris, Berges, Levrault & Cie, 1881.

Rapid renal failure with oliguria occurred in cases 30, 32 and 33, in which the renal pathologic process proved to be either a subacute or a congestive state. In cases 32 and 33 the concentration of potassium in the serum was distinctly increased to 34.2 and 27.1 mg. in 100 cc. respectively and renal failure was due to congestion of the kidneys. Two previous groups of observers have made similar observations; that is, the concentration of potassium in the serum may become distinctly increased in patients who are suffering from myocardial decompensation with congestion of the kidneys. In 1922 Olmer, Payan and Berthier [16] reported on 3 such patients. Later, in 1932, Scholtz [17] especially mentioned 3 similar cases and commented on the absence of a renal pathologic process other than the passive congestion. In case 30 (tables 2 and 3), however, rapid renal failure and oliguria did develop, but a high

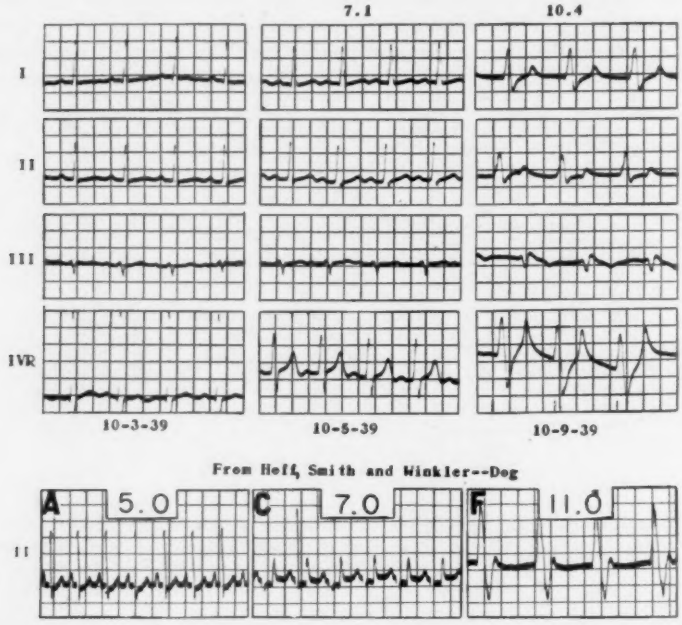

Fig. 6.—Electrocardiograms made in case 15, in which fatal uremia with pericarditis developed and in which the value for serum potassium was high, compared with the electrocardiogram of a dog poisoned by potassium chloride. At the time the first tracing was made pericarditis was present, but it had no characteristic representation in the electrocardiogram. The changes in the T waves in the second tracing, particularly in the fourth lead, are similar to those which we have obtained after the administration of potassium to man. The last tracing, without P waves and with an intraventricular conduction defect, is most unusual, and we were impressed by its similarity to the tracings published by Hoff, Smith and Winkler [10] in their report on experimental intoxication with potassium (p. 608). Above the second and third tracings made in our case are given the potassium content of the serum in milliequivalents, as also noted, below, in the three tracings of the dog.

16. Olmer, D.; Payan, L., and Berthier, J.: Le potassium du sérum sanguin dans l'insuffisance rénale, Compt. rend. Soc. de biol. **87**:867-869 (Sept. 15) 1922.

17. Scholtz, H. G.: Ueber den Calcium- und Kaliumgehalt im Blutserum und die Ultrafiltierbarkeit dieser Minerale bein Niereninsuffizienz, Deutsches Arch. f. klin. Med. **172**:472-482, 1932.

concentration of potassium in the serum did not. The patient had had marked oliguria for four days previous to admission; and during three of the days during which he was under observation in the hospital the daily twenty-four hour output of urine totaled 150 cc., none and 15 cc. respectively. In spite of this pronounced oliguria and anuria, the concentration of potassium in the serum on the morning of the day before death was 19.7 mg. per hundred cubic centimeters. This result is perhaps comparable to that obtained in one experiment on a series of dogs rendered anuric by mercury bichloride in the study by Hoff, Smith and Winkler.[10]

The low initial concentration of potassium in the serum in case 31 is of especial interest. This patient, a physician, had been vomiting frequently for several weeks before his admission, and he himself suggested the possibility of an intrinsic gastric lesion. No such lesion was present. The low intake of food and loss of potassium in the vomitus probably played an important role in his having a subnormal concentration of serum potassium, 12.8 mg. per hundred cubic centimeters, for at that time his renal function was not markedly disturbed. With the subsequent rapid development of oliguria and severe renal insufficiency due to arterial thrombosis in the kidneys, the concentration of urea in the blood rose to 390 mg. and the serum potassium to a normal concentration, of 17.9 mg.[18] Snapper[19] reported a similar low concentration of serum potassium in a case of acute mercury poisoning with renal insufficiency.

A decided improvement in renal function took place in a single instance in the present series (case 10) while the patient was under observation. The improvement in renal excretion was accompanied with a distinct decrease in the concentration of serum potassium from an abnormally high (27.3 mg.) to a normal level (20.4 mg.).[20] Scholtz reported a similar experience in 1 of his cases of secondary contracted kidney. Since this sequence of events occurred in our case 10 and in that of Scholtz, in both of which chronic diffuse nephritis was present, it seems reasonable to suppose that it may happen more frequently in the receding phase of severe acute renal insufficiency. A somewhat different result occurred in case 21. Some improvement in renal function, as indicated by a decrease of 60 mg. in the concentration of blood urea, was accompanied not by a decrease but by a slight increase in serum potassium.

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18. Rosenberg, E. F.; Keith, N. M., and Wagener, H. P.: Diffuse Arterial Disease with Hypertension: Two Unusual Cases of Contrasting Types, Arch. Int. Med. **62**:461-481 (Sept.) 1938.

19. Snapper, I.: Chinese Lessons to Western Medicine, New York, Interscience Publishers, Inc., 1941.

20. Treatment during this period in case 10 consisted of ingestion of a diet containing approximately 2,000 calories, 60 Gm. of protein and 3 to 5 Gm. of sodium chloride. The intake of fluid averaged 2,000 to 3,000 cc.; 1,000 cc. of this daily intake of fluid often was injected intravenously and contained 100 Gm. of dextrose or 9 Gm. of sodium chloride, or both substances in these amounts. After these therapeutic measures polyuria, improvement in renal function and a decrease in serum potassium took place. Similar treatment was carried out in many other cases of this series without demonstrable effect on the concentration of potassium in the blood serum. In addition, blood was transfused to several of our patients. In case 15, in which severe uremia was present, blood was transfused on the third hospital day. Estimation of the potassium content of the serum next morning revealed a high value, of 27.8 mg. per hundred cubic centimeters. Four days later it had increased to 40.9 mg. We do not think that the transfused blood had a causal relation to the increase in serum potassium, because in a subsequent case the values for serum potassium before and after transfusion of blood were identical. In neither this patient's case (case 15) nor in others did we make a systematic study of the effect of transfusion on the constituents of the blood. Our available data failed to reveal any constant change in the potassium content of serum due to the transfusion of blood.

Rabinowitch has briefly discussed the potassium: sodium ratio in serum from patients with cardiorenal disease. The mean normal ratio as recorded by Macallum [21] is 0.0611. Rabinowitch found an elevation to more than 0.0700 in only 5 of 14 cases, in all of which the blood urea nitrogen was more than 90 mg. per hundred cubic centimeters (a blood urea concentration of more than 190 mg.). The ratio was calculated in 26 cases in our series. Normal ratios [22] were present at some time in 11 cases, and increased ratios were observed in 18. It is apparent that there was a tendency toward increased potassium: sodium ratios in many of our cases, but there are definite exceptions when individual cases are considered. It should also be pointed out that the normal ratio was found in cases in which there was a normal concentration of potassium in the serum and the increased ratio was found in those in which there was an abnormally high concentration of potassium in the serum. Therefore this ratio appears to vary directly according to the concentration of potassium present.

The ingestion of a potassium salt may cause a distinct temporary increase in serum potassium, both in the normal and in the sick person, as previously noted by Thomson,[23] Keith and Binger [24] and others.[25] Such was the succession of events in cases 27, 28 and 29 (table 4). The ingestion of 15 Gm. of potassium nitrate (case 32) four days before the high concentration of potassium was observed in the serum probably played a very minor role in causing an increase to 34.2 mg. per hundred cubic centimeters (table 4). A brief summary of the history and course in the hospital in case 28 follows:

A man 45 years old was admitted to the clinic on Sept. 28, 1933, complaining of swelling of the feet, scrotum, abdomen and face. He said the condition had been present for four weeks. For six years he had noted intermittent nausea and vomiting within two hours after eating but had had no pain. He had noted occasional headache and increased fatigue, and for the four weeks preceding admission there had been increasing edema, decreased urinary output and albuminuria. Vision was normal. Physical examination revealed edema, grade 3, of the feet, legs and scrotum, suggestive early ascites and a puffy appearance of the face. Urinalysis disclosed a specific gravity of 1.007 to 1.013, albuminuria of grade 1 to 2, pyuria of grade 1 to 2, no sugar, no erythrocytes and no casts. Thoracentesis on the right side was necessary on two occasions, and abdominal paracentesis was necessary on six occasions. The patient was dismissed on March 19, 1934 (one hundred and seventy-first hospital day).

Studies of potassium in this case showed that during the eleven day interval between the determinations of values of serum potassium 22.6 and 33.1 mg. per hundred cubic centimeters the patient received a total of 46 Gm. of potassium nitrate. During the thirty day interval between the determinations of serum potassium concentrations of 33.1 and 23.1 mg. the patient received a total of 66 Gm. of potassium nitrate, of which only 12 Gm. was given in the twenty days immediately preceding determination of the value of 23.1 mg.

The increase of potassium in the serum in case 27 was particularly striking. Ninety minutes after the ingestion of 5 Gm. of potassium bicarbonate the concentration in the serum increased to 37.3 mg. from a previous level of 31 mg. per hundred cubic centimeters. We have since observed that when a young woman

21. Macallum, A. B.: The Ancient Factors in the Relations Between Blood Plasma and the Kidneys, Tr. Coll. Physicians, Philadelphia **39**:286-299, 1917.

22. The normal range was calculated by taking the quotients resulting from dividing the minimal and maximal normal serum potassium values by the maximal and minimal normal serum sodium values respectively; for example, 17 divided by 359 = 0.047 and 21.3 by 315 = 0.068.

23. Thomson, W. A. R.: The Effect of Potassium on the Heart in Man, Brit. Heart J. **1**: 269-282 (Oct.) 1939.

24. Keith, N. M., and Binger, M. W.: Diuretic Action of Potassium Salts, J. A. M. A. **105**:1584-1590 (Nov. 16) 1935.

25. Scudder, J.: Shock: Blood Studies as a Guide to Therapy, Philadelphia, J. B. Lippincott Company, 1940.

(not included in this series) who had a similar type of chronic glomerulonephritis and a similar grade of renal insufficiency was given 5 Gm. of potassium bicarbonate by mouth within ninety minutes the concentration of potassium increased from a control level of 26.7 mg. to 37.1 mg. In both these patients the tolerance for potassium was distinctly reduced. Zwemer and Truszkowski [26] observed in Addison's disease a similar reduction in the tolerance for potassium. The effect of the administration of a potassium salt by vein was observed in a single patient (case 6 in table 4). In this patient on the morning of the seventeenth hospital day, the concentration of urea in the blood was increased to 336 mg., whereas the value for potassium in the serum was normal, or 18.9 mg. During the evening of the eighteenth hospital day the patient received 900 cc. of an 0.8 per cent solution of

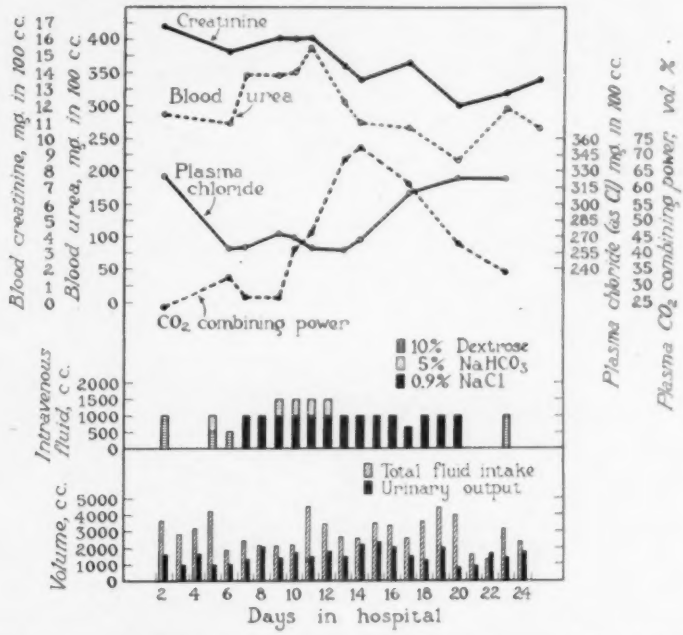

Fig. 7 (case 11).—Variations in the concentration of urea and creatinine in whole blood and of chloride and carbon dioxide-combining power in plasma. Intake of fluid, including solutions injected intravenously, and output of urine are shown.

potassium chloride (7.2 Gm. of potassium chloride) intravenously. On the morning of the twentieth day, thirty-six hours after the injection, the value for potassium in the serum was 22.4 mg. per hundred cubic centimeters. Thus, we found that the intravenous administration of a considerable amount of potassium chloride to a patient who has serious renal insufficiency does not necessarily lead to a sustained high level of the potassium in the serum.

Comparative Chemical Observations in the Blood and Urine.—Quantitative estimations were made of certain constituents in the urine and blood in case 11.

26. Zwemer, R. L., and Truszkowski, R.: Factors Affecting Human Potassium Tolerance, Proc. Soc. Exper. Biol. & Med. **35**:424-426 (Dec.) 1936.

These data afforded us a unique opportunity to compare, for example, the concentrations of urea and creatinine in whole blood and potassium in blood serum with the concentrations of these substances in the urine (figs. 7 and 8, tables 5 and 6). On the fourteenth day of observation in the hospital blood was withdrawn from a vein in the arm and urine was obtained from the bladder by catheter a few minutes later. The concentrations of urea and creatinine in the urine were approximately twice those in the blood, whereas the values for potassium were almost identical: 17 mg. per hundred cubic centimeters in the urine and 21 mg. in the blood serum. This observation in regard to potassium suggested a process of renal filtration. On

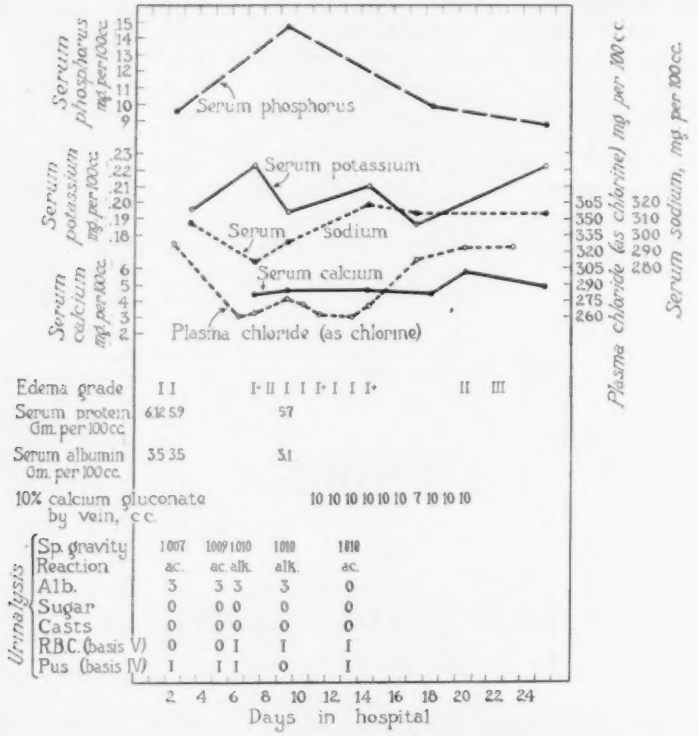

Fig. 8 (case 11).—Variations in the concentration of certain electrolytes, protein and albumin in the serum. Grade of edema and results of routine urinalysis are depicted.

the other hand, similar data obtained from the twentieth to the twenty-fourth day offered evidence that this same diseased kidney could a few days later concentrate the potassium in the serum several times and thus readily bring about excretion of it. During the latter period there was an increased formation and renal excretion of urea, creatinine, sulfate and potassium, most probably due to breakdown of protein, since pulmonary edema developed at this time and the patient's temperature increased to 102 F. (38.8 C.). However, the concentration and output of potassium in the urine increased relatively to a greater degree than those of the other three urinary constituents. It is of interest that this rather striking increase in the excretion of potassium by the kidney was accompanied by only slight changes in

the concentration of potassium in the serum: 21, 18.7 and 22.2 mg. In 1921 Kramer and Tisdall in the original description of their micromethod for determining potassium in the serum reported increases in the concentration of potassium in

TABLE 5.—*Certain Constituents of Urine in Case 11; Collection of Urine for Twenty-Four Hour Period*

Hospital Day	Volume, Cc.	Specific Gravity	Inorganic Sulfate		Urea		Creatinine		Nonprotein Nitrogen		Total Protein *		Potassium		Comment
			Gm. per 100 Cc.	Total, Gm.	Gm. per 100 Cc.	Total, Gm.	Gm. per 100 Cc.	Total, Gm.	Gm. per 100 Cc.	Total, Gm.	Gm. per 100 Cc.	Total, Gm.	Gm. per 100 Cc.	Total, Gm.	
14	555†	1.011	0.038	0.21	0.58	3.20	0.031	0.17	0.31	1.70	0.27	1.50	0.017	0.09	
17	1,390	1.010	0.036	0.50	0.48	6.70	0.033	0.46	0.29	4.00	0.23	3.20	0.013	0.18	
18	1,170	1.010	0.036	0.42	0.54	6.30	0.034	0.40	0.30	3.50	0.33	3.90	0.010	0.12	
19	1,910	1.010	0.036	0.69	0.55	10.50	0.034	0.65	0.31	5.90	0.33	6.30	0.012	0.23	
20	860	1.010	0.043	0.37	0.54	4.60	0.034	0.29	0.32	2.80	0.35	3.00	0.015	0.13	Acute pulmonary edema developed; temp. 98.6 F.; 1,000 cc. 0.9% NaCl i.v.
21	860	1.011	0.053	0.46	0.55	4.70	0.038	0.33	0.33	2.80	0.43	3.70	0.068	0.58	Pulmonary edema with bloody sputum; temp. 102 F.
22	1,510	1.010	0.031	0.47	0.57	8.60	0.039	0.59	0.37	5.60	0.53	8.00	0.043	0.65	Condition improved; temp. 100 F.; less orthopnea
23	1,400	1.010	0.053	0.74	0.55	7.70	0.034	0.48	0.33	4.60	0.47	6.60	0.050	0.70	Much improved; temp. 98 F.
24‡	1,650	1.010	0.055	1.00	0.52	9.60	0.036	0.67	0.33	6.10	0.35	6.50	0.045	0.83	Temp. 98 F.

* Estimated by subtracting the nonprotein nitrogen from the total nitrogen and multiplying the result by 6.25. The nonprotein nitrogen was estimated after precipitating the protein with Folin's tungstic acid reagent.

† Single catheterized specimen only; incomplete twenty-four hour collection.

‡ The patient was discharged on the twenty-fifth hospital day, and death occurred at his home six days later.

TABLE 6.—*Comparison of the Concentration of Certain Constituents of Blood and Urine*

Case	Hospital Day	Mg. per 100 Cc.					
		Urea		Creatinine		Potassium	
		Blood	Urine	Blood	Urine	Serum	Urine
7	23	386	....	10.4	..	25.4	150*
	45	358	865	6.4	..	23.9	149*
11	14	273	580	13.6	31	21.0	17*
	17	267	480	14.6	33	18.7	13
	20	216	540	12.0	34	....	15
	21	....	550	....	38	....	68
	22	....	570	....	39	....	43
	23	294	550	12.8	34	....	50
	24	....	520	....	36	22.2	45

* Single specimen of urine obtained by catheter.

the serum of children who had various infectious diseases and associated fever. Zwemer, Sims and Coggeshall [27] also observed an increase in the value of serum potassium during the period of chills and fever in patients suffering from malaria.

In case 7 (table 6) simultaneous determinations of the concentration of potassium in the blood serum and urine were made on two occasions. On the

27. Zwemer, R. L.; Sims, E. A. H., and Coggeshall, L. T.: Plasma Potassium Level During Malaria Infection in Monkeys and Man, Am. J. Trop. Med. **20**:687-701 (Sept.) 1940.

twenty-third hospital day a specimen of urine (260 cc. obtained by catheter) contained 150 mg. of potassium per hundred cubic centimeters, whereas the value for potassium in the serum was 25.4 mg. Similar observations were made on the forty-fifth hospital day (table 6), or two weeks before the patient died. These

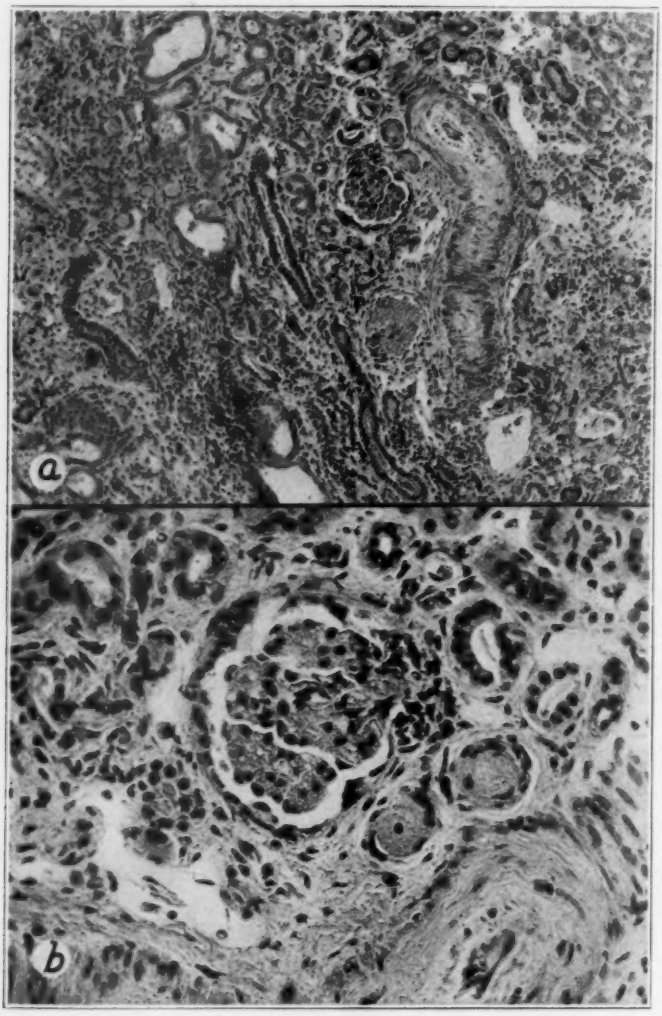

Fig. 9 (case 7).—Sections of kidney (hematoxylin and eosin; *a*, × 100; *b*, × 320). Pronounced arteriosclerosis and arteriolosclerosis, atrophy and dilatation of tubules and hyalinization of some glomeruli, whereas others appear only slightly injured. There is an increase in interstitial connective tissue.

results indicate that the kidneys of this patient were able to excrete potassium in the urine at a concentration six times that of the blood serum. However, this patient died thirteen days later, and chronic histopathologic changes in the kidney

were very noticeable (fig. 9, case 7). Almost identical observations in regard to the excretion of potassium were obtained in the study of case 26. In this case even when the concentration of potassium in the serum reached 31.7 mg. the concentration in the urine was 207 mg., or six times greater than that in the serum (fig. 4, twenty-second day).

The continued functional ability of a seriously damaged kidney to excrete and concentrate potassium and urea is of further interest in view of some results which we obtained in the study of the blood and urine of 3 patients, not included in the present series, who had uremia and who died within two and a half to thirty hours after specimens of blood and urine were withdrawn simultaneously for determinations of urea. Blood was withdrawn by needle from a vein in the elbow, and urine was secured by catheter from the bladder. The concentrations of urea in the blood plasma were 369, 519 and 627 mg. per hundred cubic centimeters, and the corresponding concentrations in the urine were 626, 785, and 952 mg. These observations concerning urea and those noted previously concerning potassium reveal that even at the very termination in a case of chronic diffuse nephritis the renal parenchyma may be capable of concentrating the urea and potassium of the circulating plasma.

Comparison of the Clearance by the Kidney of Potassium and of Urea.—Our experience in cases 11 and 7 in regard to the excretion of potassium by the kidney led us to determine the actual clearance of the blood serum of potassium into the urine and to compare its clearance with that of urea during a short period, of approximately one hour.[28] The clearances were determined in the early morning before breakfast. The results observed in ten clearance periods, in 8 of our cases, are listed in table 7. The most striking result is that urea clearance was markedly reduced in every case, whereas clearance of potassium was reduced below the minimal normal value in only 2 instances (cases 10 and 19). In case 19 renal dysfunction was pronounced and the concentration of potassium in the urine was the lowest observed in the cases in which studies of clearance were made; in fact, the concentration of potassium was approximately isotonic with that in the serum. A similar observation was made in case 11 on the fourteenth hospital day (tables 5 and 6). In the second instance of decreased potassium clearance (case 10) the clearance was reduced to 5 cc., the minimal normal value being 6 cc. However, when the test was repeated seven days later, the clearance had increased to 7 cc. Thus, in only a single instance (case 19) was the clearance of potassium found to be distinctly less than normal; this result most likely is to be explained by the histopathologic changes observed in this case. There was marked destruction of the renal parenchyma (fig. 10). It was pointed out previously that the oral ingestion of 5 Gm. of potassium bicarbonate in case 27 had led to a rapid increase in the

28. Since pus cells frequently were present in the urinary sediment in our cases, and since these cells contain intracellular potassium, the question arose as to whether the presence of such cells in the urine augmented the actual quantity of potassium excreted by the kidneys. The urine was especially examined in 5 cases with regard to this point. In case 9 the concentration of potassium in the urine was very low, yet the sediment contained large numbers of leukocytes. In case 27 clearance was estimated twice; in one specimen of urine there were no leukocytes; in the other 20 to 50 cells to a field were found with the high-power lens. Yet the concentrations of potassium in the two specimens were practically identical. We then analyzed a sample of well shaken urine and also a sample of the same urine obtained from the upper portion of the tube after rapid centrifuging for several minutes. The concentration of potassium was the same in the two samples. The results of this experiment, carried out on urine from 5 patients, were similar. There were never more than a few erythrocytes in the sediment; so their presence would not have altered the concentration of potassium. The foregoing evidence is convincing that the concentration of potassium in the urine was not increased by the presence of leukocytes.

concentration of serum potassium from a previous high level. Clearance of potassium and urea was determined at this time, and it will be noted that the clearance of both was reduced when compared with the clearance obtained during a control period three days before. This result might have been due to a reduction in the volume of urine, but it does suggest the possibility that the ingestion of 5 Gm. of potassium bicarbonate had produced a temporary toxic effect on the kidneys of this patient.

Our results, therefore, in study of the clearances of potassium in severe chronic renal insufficiency compare closely with those of Winkler, Hoff and Smith.[29] These observers pointed out that the presence of a normal fasting clearance of potassium in a patient who has severe chronic nephritis suggests that kidneys so affected can excrete the basal daily amount of potassium resulting from tissue catabolism. However, when an extra amount of potassium must of necessity be excreted, these diseased kidneys excrete it more slowly than normal ones, and if this extra load continues there will be a slow accumulation of potassium within the body, so that

TABLE 7.—*Clearance of Potassium and Urea in Severe Chronic Renal Insufficiency*

					Urine			Whole Blood and Serum †		Whole Blood and Serum Clearance ‡			
										Potassium		Urea	
										$\frac{U \times V}{S} \times \frac{1.73}{B.S.‡}$		$\frac{U \times V}{B} \times \frac{1.73}{B.S.‡}$	
Case	Age, Yr.	Sex	Body Surface, Square Meters	Experimental Period, Min.*	Minute Volume (V), Cc.	Potassium (U), Gm. per 100 Cc.	Urea (U), Gm. per 100 Cc.	Potassium (S), Mg. per 100 Cc.	Urea (B), Mg. per 100 Cc.	Cc. per Min.		Cc. per Min.	
8	27	F	1.61§	60	1.05	0.129	0.743	17.8	294	8		3	
10‖	64	F	1.58	60	1.6	0.082	0.503	26.7	146	5		6	
				60	2.1	0.090	0.451	27.3	144	7		8	
16	31	F	1.54	68	1.97	0.064	0.409	21.4	170	6		5	
19	31	M	2.05	71	2.18	0.023	0.766	17.8	356	2		4	
20	48	F	1.69	60	3.4	0.080	0.502	21.4	204	13		9	
21	33	F	1.52	60	3.5	0.045	0.315	24.6	180	7		7	
22	20	M	1.66	60	1.6	0.094	0.725	21.4	348	7		3	
27‖	16	F	1.59	60	2.5	0.152	0.702	32.9	124	13		15	
				65¶	0.95	0.247	0.725	37.3	118	7		6	

* Urine collected by catheter at beginning and end of period in the morning before breakfast.
† Blood obtained at midperiod of experiment. Estimation of urea done on oxalated whole blood.
‡ Corrected for body surface of 1.73 square meters. B.S. means body surface.
§ Approximate.
‖ Two experiments in case 10 and case 27, seven and three days apart, respectively.
¶ Patient took 5.0 Gm. of potassium bicarbonate before the experiment.

actual retention will take place. The results of Winkler, Hoff and Smith,[29] who gave extra potassium to several patients with nephritis, are in harmony with this viewpoint. Previous support for the occurrence of such a series of events was given in 1913 by Blumenfeldt,[30] who found that potassium was being distinctly retained in a patient who had cardiac edema and chronic diffuse nephritis. However, in 1935 MacKay and Butler carried out a detailed metabolic study of a patient who had terminal chronic glomerulonephritis, and in whom edema was limited to the region of the ankles.[31] In addition to a known diet, these investigators

29. Winkler, A. W.; Hoff, H. E., and Smith, P. K.: The Toxicity of Orally Administered Potassium Salts in Renal Insufficiency, J. Clin. Investigation **20**:119-126 (March) 1941.

30. Blumenfeldt, E.: Beiträge zur Kaliausscheidung unter normalen und pathologischen Verhältnissen, Ztschr. f. exper. Path. u. Therap. **12**:523-528 (Feb. 22) 1913.

31. (*a*) MacKay, E. M., and Butler, A. M.: Studies of Sodium and Potassium Metabolism: The Effect of Potassium on the Sodium and Water Balances in Normal Subjects and Patients with Bright's Disease, J. Clin. Investigation **14**:923-939 (Nov.) 1935. (*b*) Van Slyke, D. D.; Stillman, E.; Möller, E.; Ehrich, W.; McIntosh, J. F.; Leiter, L.; MacKay, E. M.; Hannon, R. R.; Moore, N. S., and Johnston, C.: Observations on the Courses of Different Types of Bright's Disease, and on the Resultant Changes in Renal Anatomy, Medicine **9**:257-386 (Sept.) 1930.

administered 5 to 10 Gm. of potassium chloride daily to their patient for eight days. During this period they demonstrated that considerable retention of potassium occurred. No estimations of the concentration of potassium in the serum of this patient or in that of Blumenfeldt's patient were recorded by the investigators in question. Therefore, the question as to whether or not such a degree of retention

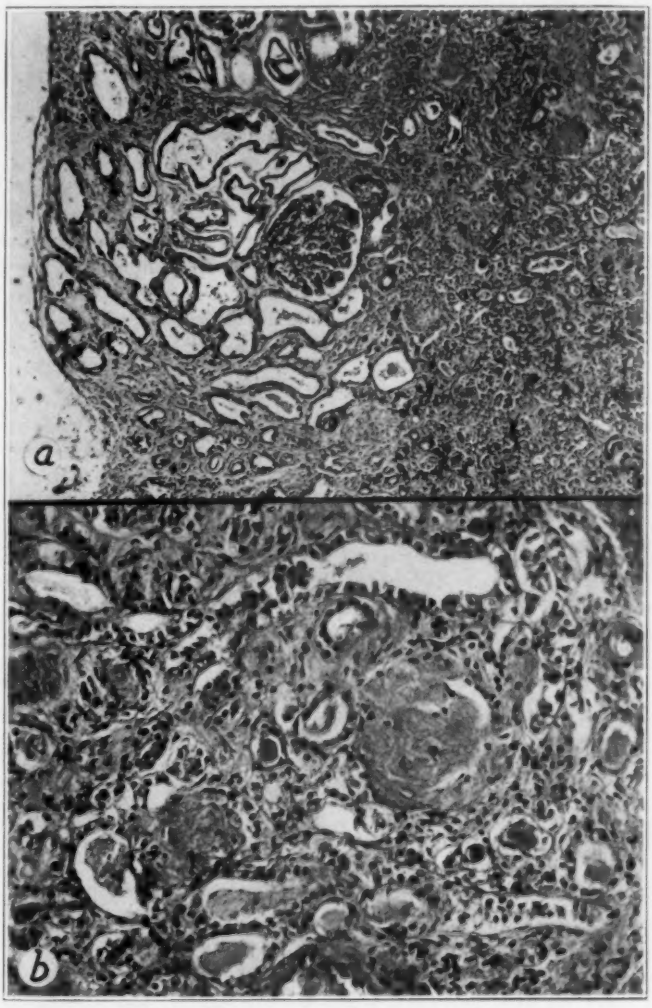

Fig. 10 (case 19).—Sections of kidney (hematoxylin and eosin; *a*, × 50; *b*, × 150). The patient died at home thirty-two days after dismissal from the hospital. No normal glomeruli are seen; most of them have been transformed into hyalinized masses of connective tissue. Some of the glomeruli have undergone necrosis; others reveal cellular proliferation. Many of the tubules are dilated and filled with debris; many are atrophied or undergoing necrosis. The arteries and arterioles are greatly thickened, some of them to the point of occlusion.

of potassium could lead to a distinct sustained increase of potassium in the serum was left unanswered.

COMMENT

It seems clear that potassium metabolism may be disturbed in the presence of renal disease. However, at present this disturbance of potassium metabolism cannot be as readily demonstrated as can that of some other substances actively excreted by the kidney. The observations of previous investigators and the results of the present study agree in revealing that a single estimation of the concentration of serum potassium in the presence of severe renal insufficiency may give a result that is normal, increased or decreased. But when several estimations are made of the serum of the same patient during the course of renal insufficiency, as was done on the serum of many of our patients, it is evident that at some time the content of potassium in the serum may become abnormally high. In such an instance, again, any factor that decreases the intake or disturbs the output of potassium, such as anorexia, vomiting [32] or diarrhea, may lower its concentration in the blood serum. Other factors that perhaps prevent a steadily increasing retention of potassium in the blood by severely damaged kidneys are the relatively good fasting urinary clearance of potassium and the development of polyuria. The increased output of water in the presence of chronic renal disease may permit the excretion of potassium at a low rate, but in total amounts which are nevertheless sufficient in twenty-four hours to keep the concentration in the serum from increasing to abnormal levels.

A review of the observations of others on renal disease and the results in this series of cases indicate that high values for potassium in the serum are more usually obtained when rapid renal failure occurs. The closer renal insufficiency is to total loss of renal function, the more likely it seems that the excretion of potassium is disturbed. Such rapid renal failure may take place in acute, subacute and congestive renal disease; it also may occur in chronic nephritis, especially during an acute exacerbation or in the terminal phase. Indeed, an abnormally high value for potassium in the serum may possibly indicate that an acute phase is present during the course of chronic renal disease.

Previous observers have stressed the presence of marked oliguria or anuria when the concentration of potassium in the serum increases. We have had a similar experience but have also observed in the serum of several patients an increase in serum potassium to between 30 and 40 mg. per hundred cubic centimeters at the same time that a considerable volume of urine was being excreted. This observation supports the viewpoint that in the presence of severe renal insufficiency, when the output of water is ample, there may be at a given time a greater disturbance in the excretion of a single substance (in this instance potassium) than in the excretion of others.

The occurrence of a high value for potassium in the serum of human beings who have congestion of the kidneys and oliguria seems to be of serious import and indicative of the renal retention of potassium. In this connection the results of Addis and Lew [33] in experimental studies seem to be significant. They have shown that congestion of the kidneys of the rat produced by ligation of the inferior vena cava above the renal veins gives rise to oliguria and severe acute renal insufficiency. With the rapid establishment of collateral venous circulation, however, the renal congestion soon disappears, and within seven days normal renal function is restored. If before and during the acute congestive phase a potassium salt was

32. Falconer, M. A.; Osterberg, A. E., and Bargen, J. A.: Intestinal Obstruction in Man: Alterations in the Serum Bases and Their Significance, Arch. Surg. **38**:869-885 (May) 1939.

33. Addis, T., and Lew, W.: Diet and Death in Acute Uremia, J. Clin. Investigation **18**:773-775 (Nov.) 1939.

ingested, the mortality rate among these rats reached 50 per cent. Estimations of the concentration of potassium in the serum of the rats which had been fed potassium were not made by these investigators, but it naturally may be presumed that it was elevated.

Experiments in the laboratory reveal that bilateral nephrectomy, bilateral ligation of the ureters, bilateral exposure to roentgen rays and acute nephritis produced by uranium and mercury bichloride lead to an abnormal increase in serum potassium, or, in other words, to retention of potassium in the blood serum. Similar reactions are to be expected in acute experimental congestion of the kidneys. Thus, there is ample experimental evidence that potassium may be abnormally retained in the blood stream by acutely decompensated kidneys. This fact leads to consideration of the toxicity of potassium salts when given to animals which have so-called uranium nephritis. Smillie [34] in 1915 reported results of such experiments in rabbits and noted that sudden death frequently occurred. He attributed these fatalities to the rapid retention of potassium in the blood and its subsequent toxic action on the heart, but he did not actually estimate the concentration of potassium in the blood. In this connection the results of experiments by Bergman and Drury [35] in bilateral nephrectomized rats appear to be important. They found that the ingestion of ash containing a considerable amount of potassium decidedly reduced the survival period when it was compared with the survival period of control animals. Hoff and his co-workers also showed that when a potassium salt was given to a dog which had anuria due to either bilateral nephrectomy or ligation of the ureters, the survival period was decreased. Hoff and his associates further revealed by means of electrocardiographic studies that death among these anuric animals was due to a great increase in the concentration of potassium in the blood plasma, which finally caused cardiac failure. To date the evidence of retention of potassium in cases of severe acute clinical renal damage is meager. In Darrow's case in which a child had acute glomerulonephritis (reported by Hoff and associates) the value for potassium in the serum was high. Beall, Bywaters, Belsey and Miles [36] also found that the value for potassium in the serum was very high in a case, complicated by renal failure, after injury to a leg had been inflicted by crushing. Both these observations are of interest in this connection. Therefore, cases of acute renal insufficiency, including cases of acute glomerulonephritis and the toxic nephritides, such as acute intoxication with mercury bichloride or with bismuth, offer a unique opportunity for further study of the potassium problem in relation to renal disease. Future investigation in cases in which the condition is acute should include frequent estimations of the concentration of potassium in the serum and simultaneous electrocardiographic tracings. Our observations in case 15 during the terminal phase of chronic renal disease indicate that the electrocardiogram may reveal alterations very suggestive of intoxication with potassium.

In contrast to the probable toxic effects of a potassium salt in patients who have severe renal failure is the well recognized clinical experience of many observers that large doses of such a salt may be ingested by patients suffering from chronic nephritis with edema without noticeable harmful results; this was the experience

34. Smillie, W. G.: Potassium Poisoning in Nephritis, Arch. Int. Med. **16**:330-339 (Aug.) 1915.

35. Bergman, H. C., and Drury, D. R.: A Study of Acute Renal Insufficiency, J. Clin. Investigation **18**:777-781 (Nov.) 1939.

36. Beall, D.; Bywaters, E. G. L.; Belsey, R. H. R., and Miles, J. A. R.: A Case of Crush Injury with Renal Failure, Brit. M. J. **1**:432-434 (March 22) 1941.

of Wilks and Taylor [37] in 1863, our experience in 1935 [24] and in 2 cases of the present series and also that of Winkler, Hoff and Smith [29] during the past year (1941). The actual doses that have produced toxic effects on the kidney in 2 normal men under our care were very much larger than those prescribed in clinical medicine.[39] This also applies to experiments conducted on 3 normal men in whom dehydration as well as reduced renal function resulted from the ingestion of large doses of a potassium salt.[39c] There are, no doubt, patients who have chronic nephritis with moderate retention of urea and an increased concentration of potassium in the serum, similar to that in our cases 24, 26 and 27, to whom it may be dangerous to administer moderate doses of a potassium salt, but they are probably few. We had previously cautioned against the administration of potassium salts to patients who have nephritic edema and a concentration of urea in the blood of more than 100 mg. per hundred cubic centimeters. That some of these patients may have a lessened tolerance for potassium and even an increased value for potassium in the serum lends support to such a precaution. It seems clear, therefore, that a persistently high value for potassium in the serum is of serious prognostic import in any case of renal disease. Its presence in nephritic patients during an acute phase, in patients who have subacute or chronic processes associated with edema or in patients suffering from cardiac disease with severe passive congestion should forbid any sort of diuretic therapy which includes the administration of a potassium salt, an acid-producing salt or an organic mercury compound. In such cases the use of any of these substances may lead to serious complications.

In addition to renal insufficiency, alterations in metabolism may cause an abnormal increase in potassium in the serum, for example, when increased catabolism occurs, as in fasting or when fever is present. In these conditions, the breakdown of tissue protein is accelerated, and an increased amount of potassium is thus liberated from tissue cells and passes into the circulation to cause an increase in the concentration of potassium. A single report by Gamble, Ross and Tisdall [40] concerning a fasting child discloses a high normal value for serum potassium, which decreased after the child had resumed the ingestion of a carbohydrate diet. In the presence of fever a series of events similar to those in fasting probably occurs, and such an explanation seems to be the most satisfactory one for our observations in case 11 of the present series. Dehydration also may play a role in causing an increase in potassium in the serum. In 1935 Keith and Binger [24] reported some interesting results of experiments conducted on 3 normal persons and a patient who had chronic polyserositis, in which dehydration apparently developed. To each of these persons was given a diet low in both mineral salts and water and also extra potassium, 50 to 80 mg. per kilogram of body weight, daily for several days. In the serum of each person an increase occurred in the concentration of potassium to 33 to 40 mg. per hundred cubic centimeters without obvious retention of potassium by the kidneys. Is it possible that in these persons the

37. Wilks, and Taylor, A. S.: Case in Which Large Quantity of Nitrate of Potash Was Taken Medicinally: Elimination of the Salt by the Urine, Guy's Hosp. Rep. **9**:173-179, 1863.

38. Footnote deleted on proof.

39. (*a*) Keith, N. M.; Osterberg, A. E., and Burchell, H. B.: Some Effects of Potassium Salts in Man, J. Pharmacol. & Exper. Therap. **72**:22-23 (May) 1941; Some Effects of Potassium Salts in Man, Ann. Int. Med. **16**:879-892 (May) 1942. (*b*) Keith, N. M., and Osterberg, A. E.: The Excretion of Potassium by the Kidney, Am. J. Physiol. **129**:395-396 (May) 1940. (*c*) Keith, N. M.; Osterberg, A. E., and King, H. E.: The Excretion of Potassium by the Normal and Diseased Kidney, Tr. A. Am. Physicians **55**:219-222, 1940.

40. Gamble, J. L.; Ross, G. S., and Tisdall, F. F.: The Metabolism of Fixed Base During Fasting, J. Biol. Chem. **57**:633-695 (Oct.) 1923.

volume of distribution of potassium throughout the body had become less because of dehydration?[41]

Since ionic equilibrium is known to be influenced by certain hormones of the glands of internal secretion, and particularly by compounds elaborated by the adrenal cortex, it seemed important to evaluate any possible relationship that might obtain between the ionic pattern of the serum in renal insufficiency and alterations in the adrenal bodies. In the presence of severe chronic renal insufficiency the content of potassium in the serum may be abnormally elevated and that of sodium reduced, a pattern similar to that seen in cases of adrenal insufficiency. We therefore examined carefully the adrenal bodies of 13 persons who had come to necropsy, and, as stated earlier in this paper, we were unable to find any gross or unmistakable histologic evidence of adrenal abnormality. Of course, negative results of histologic study do not rule out a possible functional alteration in these bodies. In certain cases in which the condition belongs to the so-called Cushing syndrome, changes occur in electrolytic metabolism, including an abnormally low concentration of potassium in the serum. This has been noted by McQuarrie, Johnson and Ziegler[42] and by Willson, Power and Kepler.[43] In none of the cases in this series did the clinical observations suggest such a syndrome, and the characteristic lesions in the adrenal cortex sometimes found in such cases were absent. In the 13 cases in which pathologic studies were carried out, however, changes in the pituitary body could not be excluded because this body was not examined by the pathologist. The evidence at hand from this study therefore does not support the viewpoint that the disturbances in potassium metabolism encountered were due to endocrine dysfunction.

The actual excretion and retention of different inorganic ions by the kidney is of great physiologic interest. Study of the individual excretion of these ions has been greatly stimulated by the development of accurate microchemical methods. For example, it is known that inorganic sulfates are readily excreted, but in a manner different from that in which chlorides are excreted. The chlorides, together with sodium, may be noticeably retained by the kidney, especially when the intake of these ions is small. The renal clearance of potassium in the starving normal person is remarkably small, being approximately 10 to 12 per cent of that of inulin. Since inulin is considered to be excreted by the kidney entirely by a process of glomerular filtration and since the potassium ion is also thought to be filtered readily by the glomeruli, the small clearance of potassium suggests that a relatively large percentage of that filtered by the glomeruli is reabsorbed by the tubules. Such a cycle of filtration and reabsorption within the kidney is analogous to the excretion of potassium into the stomach and its reabsorption into the blood from the large bowel.[44] We have obtained, however, some interesting results among normal persons in whom dehydration occurred after the ingestion of large doses of a potassium salt. The clearance of inulin decreased and that of potassium increased,

41. Winkler, A. W., and Smith, P. K.: The Apparent Volume of Distribution of Potassium Injected Intravenously, J. Biol. Chem. **124**:589-598 (Aug.) 1938. Winkler, A. W.; Hoff, H. E., and Smith, P. K.: Toxicity of Potassium in Adrenalectomized Dogs, Am. J. Physiol. **133**:494-495 (June) 1941.

42. McQuarrie, I.; Johnson, R. M., and Ziegler, M. R.: Plasma Electrolyte Disturbance in Patient with Hypercorticoadrenal Syndrome Contrasted with That Found in Addison's Disease, Endocrinology **21**:762-772 (Nov.) 1937.

43. Willson, D. M.; Power, M. H., and Kepler, E. J.: Alkalosis and Low Plasma Potassium in a Case of Cushing's Syndrome: A Metabolic Study, J. Clin. Investigation **19**:701-707 (Sept.) 1940.

44. Fenn, W. O.: The Rôle of Potassium in Physiological Processes, Physiol. Rev. **20**: 377-415 (July) 1940.

so that the potassium : inulin ratio was greater than unity, suggesting actual tubular secretion of potassium. McCance and Widdowson [45] reported a similar result in a patient who had alkalosis. The normal kidney therefore appears to play a dual role in the metabolism of potassium in that it possesses ready mechanisms for both the excretion of potassium into the urine and the reabsorption and ultimate retention of it in the blood stream. The abnormal retention of urea and potassium in the blood, the excessive excretion of sodium in the urine in the presence of adrenal insufficiency and the remarkable restoration to normal of values for these substances when an extract of the adrenal cortex is administered naturally suggest that the adrenal cortical hormone which has to do with the metabolism of water and inorganic ions may be an important regulating factor in the normal renal metabolism of potassium. Further investigation of this possible relationship between renal and adrenal functions with regard to potassium might throw light on the intracellular function of potassium in the renal tubules.

The normal kidney excretes potassium in an oscillating manner. The low clearance of potassium in fasting states suggests regulation to prevent excessive loss. On the other hand, the rapid increase in its clearance after a considerable amount of it is ingested indicates regulation to prevent excessive retention. This regulation of the renal excretion of potassium evidently plays an important role in control of the level of its concentration in the blood serum. On the basis of results of studies, such as the present one, on renal disease we have learned that the concentration of potassium in the serum is held within a rather narrow range. The highest concentration encountered in our series of patients was 41 mg. per hundred cubic centimeters, or approximately twice the normal concentration, and was found at a time when marked chronic renal insufficiency was present. The consistent ability of seriously damaged kidneys to keep up a normal fasting clearance of potassium unquestionably is one factor in the prevention of too great an increase in potassium in the serum. We know, however, that there are also extrarenal factors, such as dehydration, excessive tissue catabolism and the volume of distribution of potassium throughout body fluids and tissue cells, which may have a similar effect. One obvious reason for both these regulatory mechanisms, renal and extrarenal, is prevention of the concentration of potassium in the serum from rising too high, for there is considerable evidence that a concentration of between 40 to 60 mg. per hundred cubic centimeters may be markedly toxic to the cells of many different tissues (up to the present time this can best be demonstrated in those of the heart).

SUMMARY

Disturbances of potassium excretion are sometimes difficult to demonstrate in the presence of renal disease. They occur more frequently than has been suspected. When severe renal dysfunction develops in acute or subacute nephritis, in the terminal stage of chronic nephritis or in marked congestion of the kidney, potassium is more slowly excreted into the urine and the concentration of it in the blood serum may increase to twice the normal value. Several factors, both renal and prerenal, appear to hinder increase in the concentration of potassium in the serum, and this curb on such an increase seems to be more effective in man than in the experimental animal. When a sustained increase in serum potassium does occur in renal disease, however, it is of serious prognostic import and should forbid the therapeutic use of a potassium salt.

45. McCance, R. A., and Widdowson, E. M.: Alkalosis with Disordered Kidney Functions: Observations on a Case, Lancet **2**:247-249 (July 31) 1937.

METHODS OF CHEMICAL ANALYSIS EMPLOYED IN THE PRESENT STUDY

WHOLE BLOOD

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Urea.—Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease, and Its Use in the Determination of Urea, J. Biol. Chem. **19**:211-228, 1914.

Creatinine.—Folin, O.: Laboratory Manual of Biologic Chemistry, ed. 3, New York, D. Appleton and Company, 1922, pp. 149, 245 and 247.

PLASMA

Chloride.—Osterberg, A. E., and Schmidt, E. V.: The Estimation of Plasma Chlorides, J. Lab. & Clin. Med. **13**:172-175 (Nov.) 1927.

Carbon Dioxide-Combining Power.—Van Slyke, D. D., and Cullen, G. E.: Studies of Acidosis: I. Bicarbonate Concentration of the Blood Plasma; Its Significance and Its Determination as a Measure of Acidosis, J. Biol. Chem. **30**:289-346, 1917.

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Potassium.—Kramer, B., and Tisdall, F. F.: A Clinical Method for the Quantitative Determination of Potassium in Small amounts of Serum, J. Biol. Chem. **46**:339-349 (April) 1921.

This method in our hands has checked with gravimetric procedures. The precipitation by sodium cobaltinitrite was allowed to proceed for forty-five minutes at ice box temperature in order to obtain a good, granular precipitate. If this and other steps are rigorously adhered to, the method is satisfactory. Potassium in urine was estimated after ashing by this method.

Sodium.—Kramer, B., and Gittleman, I.: An Iodometric Method for the Determination of Sodium in Small Amounts of Serum, J. Biol. Chem. **62**:353-360 (Dec.) 1924.

Calcium.—Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**: 461-464 (March) 1925.

Phosphorus.—Kuttner, T., and Lichtenstein, L.: Micro Colorimetric Studies: II. Estimation of Phosphorus; Molybdic Acid-Stannous Chloride Reagent, J. Biol. Chem. **86**:671-676 (April) 1930.

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Potassium.—Same method as for estimation in serum except that urine is ashed before precipitation.

Total Proteins.—Macro-Kjeldahl method for estimation of total nitrogen. Estimation of nonprotein nitrogen by macro-Kjeldahl method after precipitating the protein with Folin's tungstic acid reagent method. Total proteins calculated after subtracting the nonprotein nitrogen from the total nitrogen and multiplying by 6.25.

ADRENAL CORTEX IN SYSTEMIC DISEASE

A MORPHOLOGIC STUDY

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With the extraction of an active substance by Swingle and Pfiffner [1] and Hartman and Brownell [2] in 1930 and the more recent isolation of potent crystalline compounds by Reichstein [3] and Kendall and his associates,[4] great advances have been made in the knowledge of the physiology of the cortex of the adrenal gland. The effects of its hormones are reasonably well known today. The influence of systemic disease on the morphologic appearance of the gland is, however, not widely recognized. The latter, described by many, could not have been appreciated without the benefit of the more recent advances in the knowledge of the physiology of the gland. An attempt will be made in this paper to establish correlations between changes in the morphologic aspects of the cortex and various systemic diseases.

MATERIAL

Adrenal glands were obtained from 110 routine autopsies performed at the New Haven Hospital (one to six hours after death). No glands from persons with Addison's disease or primary neoplasm of the adrenal gland are contained in the series. The organs were dissected out of their beds with a small amount of surrounding tissue, thereby avoiding trauma to the delicate glands. They were immediately placed unsectioned in 4 per cent solution of formaldehyde, where they were allowed to remain for two days. On removal, they were carefully freed of all attached tissues, gently dried with paper toweling, and weighed on a torsion balance to the nearest hundredth of a gram. (A review of the weights of adrenal glands recorded in autopsy protocols over a twenty year period in the New Haven Hospital revealed wide discrepancies. It was deemed necessary, therefore, to employ this somewhat tedious procedure to determine the significance of the weights.) Serial longitudinal sections were made of each gland, a single representative block being taken from the widest portion unless gross examination warranted taking of others. Frozen sections, cut at 10 to 20 microns, were stained with sudan III (Herxheimer)[5] and counterstained with Harris' hematoxylin. The remainder of this block was embedded in paraffin, and sections were cut at 4 to 8 microns and stained with hematoxylin and eosin.

Since it is the purpose of this paper to correlate morphologic changes of the adrenal gland with systemic diseases, a careful review was made of the clinical history and general autopsy findings in each case. Special attention was paid to metabolic disturbances known to be intimately related to disorders of adrenal function. In addition to the usual pathologic conditions seen at the autopsy table, including hypertensive cardiovascular renal disease, generalized arteriosclerosis (nonhypertensive), infectious disease, cancer and diabetes, several examples of erythroblastosis foetalis, as well as cases with clinical manifestations of adrenal insufficiency, are contained in the series.

This investigation was aided by a grant from the Commonwealth Fund.

From the Laboratory of Pathology, Yale University School of Medicine.

1. Swingle, W. W., and Pfiffner, J. J.: An Aqueous Extract of the Suprarenal Cortex Which Maintains the Life of Bilaterally Adrenalectomized Cats, Science **71**:321, 1930.

2. Hartman, F. A., and Brownell, K. A.: The Hormone of the Adrenal Cortex, Science **72**:76, 1930.

3. Reichstein, R.: Ueber Cortin, das Hormon der Nebennierenrinde, Helvet. chim. acta **19**:29, 1936.

4. Kendall, E. C.; Mason, H. L.; Hoehn, W. M., and McKenzie, B. F.: Studies in the Chemistry of the Suprarenal Cortex, Proc. Staff Meet., Mayo Clin. **12**:136, 1937.

5. Schmorl, G.: Die pathologisch-histologischen Untersuchungsmethoden, Leipzig, F. C. W. Vogel, 1934.

THE NORMAL ADRENAL GLAND

In only 3 cases included in the series could the adrenal glands be classified as normal. These were cases of sudden death occurring in previously healthy persons. The combined adrenal weights were 10.05, 9.60 and 8.79 Gm., respectively. These values conform with those of Kiyokawa,[6] Materna [7] and Kraus.[8] Other authors, on the other hand, including Scheel,[9] Schilf,[10] Jaffe and Sternberg [11] and Dietrich,[12] have reported weights of 11.2, 11.4, 13.5 and 10 to 16 Gm., respectively. Materna's figures were based on findings in 25 cases of sudden death occurring in young previously healthy males. Dietrich and Siegmund [13] considered Materna's values to be correct and concluded that the higher values of other authors were associated with prolonged disease. This point of view is substantiated in the present series, the weight of the vast majority of the glands averaging between 11 and 13.5 Gm.

The classic histologic description of the adrenal cortex divides it into three layers: zona glomerulosa, zona fasciculata and zona reticularis. Sudan imparts an orange color to all lipoids, including cholesterol. The normal cortex exhibits a typical arrangement of sudanophilic material (fig., *A*). The greatest concentration of lipoids is in the outer half of the zona fasciculata, while somewhat less is in the zona glomerulosa, and even less is present in the inner half of the zona fasciculata and the zona reticularis. This lipoid pattern was established by Mulon [14] and Landau.[15] Landau and later Zwemer [16] elaborated Gottschau's original dynamic concept that the cells composing the adrenal cortex grow by mitotic division in the outermost layer (glomerulosa) and, during their life cycle, migrate through the zona fasciculata, eventually to die in the zona reticularis. On the basis of a histochemical technic employing phenylhydrazine and digitonin to demonstrate cortical ketosteroids and cholesterol, respectively, Bennett [17] preferred to call the zona glomerulosa the presecretory layer and subdivided the zona fasciculata into the secreting and the postsecretory layer, terming the zona reticularis the senescent layer. The secreting outer half of the zona fasciculata corresponds to the area of greatest lipoid content. When these histochemical procedures are employed with selected human adrenal glands exhibiting various types of lipoid patterns, it is seen that the distribution of the ketosteroids and cholesterol corresponds closely to the intensity of the

6. Kiyokawa, W.: Die Nebennieren bei Tuberkulose, Frankfurt. Ztschr. f. Path. **29**:287, 1923.

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10. Schilf, D.: Die quantitativen Beziehungen der Nebennieren zum übrigen Körper, Ztschr. f. Konstitutionslehre **8**:507, 1923.

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12. Dietrich, A., in Henke, F., and Lubarsch, O.: Drüsen mit innerer Sekretion, in Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 964.

13. Dietrich, A., and Siegmund, H., in Henke, F., and Lubarsch, O.: Drüsen mit innerer Sekretion, in Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8.

14. Mulon, P.: Note sur la capsule surrénale du mouton, considérations histo-physiologiques, Bibliog. anat. **22**:30, 1912.

15. Landau, M.: Die Nebennierenrinde, Jena, Gustav Fischer, 1915.

16. Zwemer, R. L.: A Study of Adrenal Cortex Morphology, Am. J. Path. **12**:107, 1936.

17. Bennett, H. S.: Life History and Secretion of Cell of Adrenal Cortex of Cat, Am. J. Anat. **67**:151, 1940.

sudanophilic material. Therefore, the phenylhydrazine and digitonin technics were not employed routinely with the human material, as it was believed that the all-inclusive sudan stain served the purpose adequately.

INFECTIOUS DISEASE

The adrenal glands from 28 adults with active inflammatory diseases are included in the series. Marked enlargement of the glands was commonly seen. Their average combined weight was 15.1 Gm., the values ranging from 10.40 to 23.55 Gm. as can be seen from table 1; almost half the glands weighed more than 16.0 Gm.

Of the 28 adults, 13 had acute inflammatory diseases, including 2 with gangrenous appendicitis and peritonitis, 2 with necrotizing pneumonia, 7 with septicemia resulting from various portals of entry, 1 with interstitial myocarditis, and 1 with acute pemphigus. The average combined adrenal weight in this group was 16.6 Gm., the weight being below 15.47 Gm. in only 3 instances.

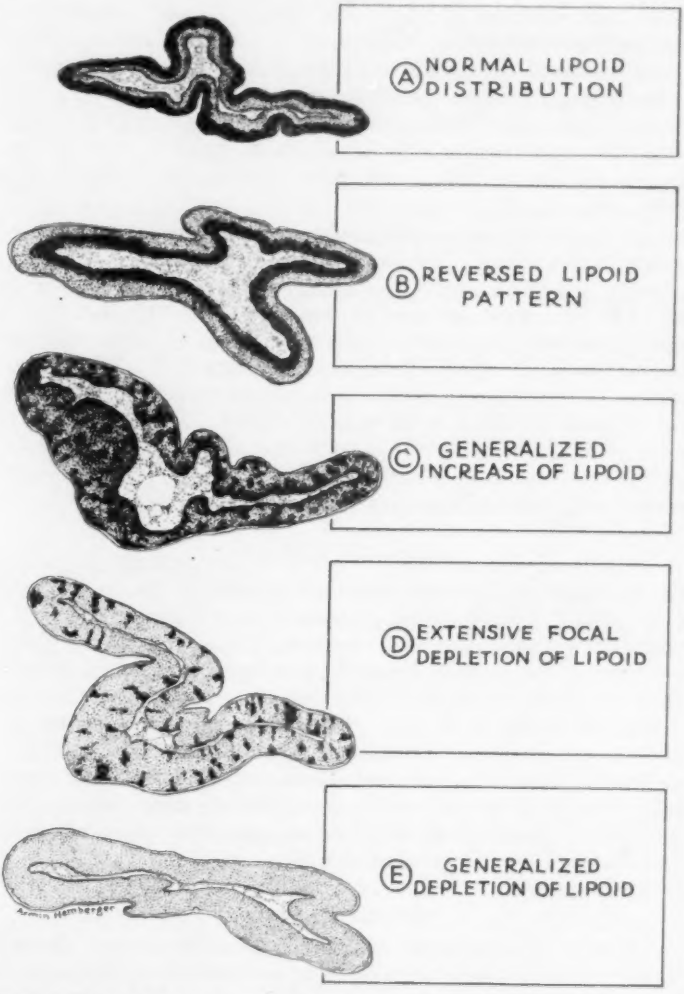
Fifteen of the 28 adults had chronic inflammatory diseases, associated with acute exacerbations in some. The average combined adrenal weight was 13.4 Gm., in contrast with 16.6 Gm., the average for the group with acute inflammatory disease.

TABLE 1.—*Weight of Combined Adrenal Glands of Twenty-Eight Adults with Active Inflammatory Disease*

Combined Adrenal Weight, Gm.	Incidence
10.40-11.95	10
13.24-13.82	3
15.47-16.00	3
16.17-18.81	9
20.41-23.55	3

Most of the adrenal glands from the group with active inflammatory diseases showed moderate to marked enlargement. The depletion of the cortical lipoid was apparent on gross examination. The usual yellow-orange color of the cortex had been transformed into pale gray. Focal patches of orange material were often seen dotting the cut surface, indicating the remnants of what was formerly a solid orange band. Microscopic examination disclosed varying degrees of lipoid depletion of the cortex associated with atypical distribution of this material; it was now in the inner instead of the outer part of the zona fasciculata (fig., *B*). In extreme cases no sudanophilic material remained in the cortex (fig., *E*). Other glands, showing less of this change, exhibited focal areas of lipoid-containing cells interspersed with fat-free areas (fig., *D*). The usual solid sudanophilic band of the cortex of the least involved glands was punctuated by circumscribed foci of lipoid depletion. The latter resembled foci of demyelination as seen in the Weigert stain. These variations in cortical lipoid content and distribution were best appreciated with the lower power lens or the naked eye. In some instances the sudanophilic material appeared as more finely particulate than usual. Central nonstaining vacuolation of some of the larger droplets of sudanophilic material was also evident. Some of the cells in the zona fasciculata possessed honeycombed cytoplasm, which proved not to be sudanophilic. Such cells were present in large numbers in some cases and were easily distinguished from the normal foamy lipoid-containing cells. In the hematoxylin eosin preparation, nests of small round cells were present in the glomerulosa layer. These cells did not contain lipoid. The cords of cells composing the zona fasciculata were slender, and the cytoplasm

of these cells was homogeneously eosinophilic, lacking the usual foamy appearance. The interstitium between the cords of the zona fasciculata was the site of edema and hyperemia. Focal hemorrhages and polymorphonuclear infiltrations were seen occasionally. No bacterial emboli were noted.


A NORMAL LIPOID DISTRIBUTION
B REVERSED LIPOID PATTERN
C GENERALIZED INCREASE OF LIPOID
D EXTENSIVE FOCAL DEPLETION OF LIPOID
E GENERALIZED DEPLETION OF LIPOID

A diagrammatic representation of the distribution of lipoid in the cortex of the adrenal gland.

All of the adrenal glands of the 28 adults with inflammatory diseases exhibited depletion of cortical lipoid or alteration in its distribution. In 21 cases these changes were associated with marked enlargement. In 5 of the remainder the glands were moderately enlarged and in 2 they were of normal size. Adenomas were found only twice.

HYPERTENSION

Twenty cases of hypertension associated with cardiac hypertrophy form the next group. In 13 of these nephrosclerosis was present. The cases were about evenly distributed between males and females, with the ages varying between 35 and 76 years. The average combined weight of the adrenal glands was 15.9 Gm., two thirds weighing more than 13.5 Gm. The abundant lipoid seen in the widened cortex on gross examination was striking. In 5 cases the adrenal glands were marked by adenomatous hyperplasia. Histologically, the inner as well as the outer zona fasciculata contained abundant lipoid. Only in 3 cases, which were complicated by inflammatory disease (phagedenic ulcers, necrotizing vascular disease and extensive myomalacia), were foci of lipoid depletion noted in the outer part of the zona fasciculata. All of the others showed a generalized increase in cortical lipoid (fig., *C*).

In the remaining 7 cases of the hypertensive group chronic glomerulonephritis or pyelonephritis was a feature. The patients were 5 females and 2 males, their ages ranging between 22 and 61 years. The average combined weight of the adrenal glands was 12.58 Gm., only one third of them exceeding 13.5 Gm. (It will be recalled that the adrenal glands of two thirds of the group with nephrosclerosis exceeded the weight of 13.5 Gm.) Excessive amounts of lipoid were present in the cortex in 4 cases. Of the 3 remaining, 1, complicated by necrotizing vascular disease, showed foci of lipoid depletion in the zona fasciculata. Similar changes without associated complicating disease were found in the second, and the normal cytoarchitecture and lipoid distribution were present in the third. It may be emphasized that adenomatous hyperplasia was present in only 1 case.

NEOPLASTIC DISEASE

Thirteen instances of neoplastic disease are included in the present study. In surveying the adrenal weights in this group it became apparent that in the cases in which cachexia was associated with neoplastic disease the adrenal glands were larger than those of the patients dying without significant loss of weight. The adrenal glands of 5 of the 6 patients of the cachetic group weighed between 11.93 and 17.85 Gm., averaging 14.30 Gm. These showed varying degrees of lipoid depletion. One pair exhibited the normal lipoid pattern. In contrast to the marked increase in adrenal weight and associated lipoid depletion seen in the cachetic patients were the normal lipoid pattern and the slight increase in adrenal weight found in the glands of patients who succumbed to neoplastic disease not associated with cachexia. The adrenal weights ranged from 11.93 to 14.41 Gm., averaging 12.46 Gm.

ATHEROSCLEROSIS

Eleven cases of atherosclerosis are included in the series. Seven of the patients were males and 4 were females. The average age of this group was 65 years. The combined adrenal weight averaged 11.6 Gm. Five pairs weighed less than 10.50 Gm., 5 ranged between 12.60 and 13.84 Gm., and only 1 pair weighed as much as 16 Gm. On microscopic examination the striking feature was the normal histologic appearance of 6 of the 11 pairs of glands. The weights of these 6 normal-appearing pairs of glands averaged approximately 10 Gm. Two other pairs exhibited a slight degree of focal depletion of lipoid in the outer part of the zona fasciculata. The remaining 3 showed an increase in the lipoid of the inner part of the zona fasciculata.

DIABETES MELLITUS

It is impossible to evaluate any changes in the adrenal cortex in the cases of this group since 8 of the 9 patients had complicating hypertension or inflammatory disease. The changes noted were those seen in connection with the latter two conditions. In the sole uncomplicated case there was no alteration in adrenal weight or histologic picture.

CIRRHOSIS

The 5 cases of cirrhosis of the liver included in this series were complicated by infectious processes, diabetes or severe long-standing anemia. Hence, the morphologic changes observed in the adrenal glands cannot be correlated with the underlying disease of the liver. All of the glands except a single pair were moderately enlarged and showed depletion of cortical lipoid or a reversal of the lipoid pattern. In the single uncomplicated case of biliary cirrhosis occurring in a 29 year old woman the adrenal glands were of normal weight and histologic appearance.

TABLE 2.—*Data on Children and Newborn Infants*

Age	Sex	Diagnosis	Adrenal Glands	
			Weight, Gm.	Histologic Change
15 mo.	M	Pneumococcic meningitis	2.84	Lipoid depletion
6 mo.	M	Retarded development (3.9 Kg.)	9.77	Lipoid depletion
3 yr.	M	Bacillary dysentery	4.22	Lipoid depletion
4 yr.	F	Encephalomyelitis	4.60	Regular lipoid pattern
		Premature Newborn Infants		
6-7th mo.	F		2.07	No lipoid in zona glomerulosa
7th mo.	F	Jaundice, aspiration	4.25	No lipoid in zona glomerulosa; hemorrhage in zona fasciculata
		Full Term Newborn Infants		
1 day	M	Diaphragmatic hernia	6.50	Minimal lipoid in outer zona glomerulosa; sudanophil band comprising inner part of zona glomerulosa and outer part of zona fasciculata; fine sudanophilic material in inner part of zona fasciculata and zona reticularis
3 days	M	Aspiration	5.70	Similar to above
11 days	M	Pneumococcic meningitis	7.48	Lipoid depletion (marked); foci of necrosis

CHILDREN AND NEWBORN INFANTS

The adrenal glands of only 2 premature infants, 3 full term newborn infants and 4 children are included in this series. Therefore, no conclusive observations can be made. The pertinent data are tabulated in table 2.

ERYTHROBLASTOSIS FOETALIS

Because of the striking enlargement of the adrenal glands, 4 examples of erythroblastosis foetalis have been grouped separately. The accurate combined adrenal weight in 2 cases was 17.30 and 12.16 Gm., and in the other 2 (collected prior to the beginning of this study), approximately 15 Gm. each. In view of these findings the determination of the water content of the enlarged glands seemed indicated. The dry weight of the adrenal glands weighing 17.30 Gm. was 3.32 Gm.; i. e., 80 per cent water content. This corresponds approximately to the 75 per cent water content found in normal weight adrenal glands of the newborn. From this it can be concluded that the increase in weight of the adrenal glands in erythroblastosis foetalis cannot be attributed to edema.

The adrenal glands in these 4 cases of erythroblastosis showed much the same microscopic picture. The lipoid pattern resembled that seen in the adrenal glands

of other newborn infants, i. e. a fat-free outer part of the zona glomerulosa, a dense band at the junction of the zona glomerulosa and the zona fasciculata, a sparse distribution of fine sudanophilic material in the zona fasciculata, and an increased concentration of lipoid in the zona reticularis. This lipoid pattern was in contradistinction to that described by Liebegott [18] and Benecke.[19] They found the outer half of the cortex free of lipoid and the inner part of the zona fasciculata and the zona reticularis heavily laden with this material. It should be stated that only in 1 case in the series were extramedullary foci of hemopoiesis found.

COMMENT

From the study of the available material it has become apparent that distinct morphologic changes occur in the cortex of the adrenal gland in various pathologic conditions: inflammatory diseases, hypertension and malnutrition. The morphologic alterations consist of an increase in the size of the glands associated with various degrees of depletion of the lipoid in the cortex. On the basis of Hass's phenylhydrazine stain employed with selected human adrenal glands, it seems reasonable to conclude that the sudanophilic material present in the cortex represents in part the adrenocortical steroids. Hence, the morphologic changes described in the cortex take on physiologic significance, lending themselves to functional interpretations.

Adrenal cortical changes in infectious diseases as described in the foregoing paragraph were known to Fraenkel [20] (grip), Thomas [21] (scarlet fever and diphtheria), Dietrich [22] and Goormaghtigh [23] (Bacillus welchii infections). Deucher [24] as well as Dietrich observed similar alterations in acute peritonitis. Kawamura [25] Albrecht and Weltmann,[26] Hueck,[27] and Wülfing [28] described depletion of cortical lipoids as a general feature of infectious diseases. I am able to confirm the changes in the amount and the arrangement of the sudanophilic substance in the cortex as well as the increase in the size of the gland in various infectious diseases. Also borne out in the present study is Wülfing's statement that the adrenocortical changes are not specific and that their intensity depends on the duration and the virulence of the infections. The average combined adrenal weight in cases of acute inflammatory disease is 15.47 Gm. whereas in cases marked by chronicity

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21. Thomas, E.: Ueber die Nebennieren der Kinder und ihre Veränderungen bei Infektionskrankheiten, Beitr. z. path. Anat. u. z. allg. Path. **50**:283, 1911.

22. Dietrich, A.: Die Nebennieren bei den Wundinfektionskrankheiten, Zentralbl. f. allg. Path. u. path. Anat. **29**:169, 1918.

23. Goormaghtigh, N.: Sur le fonctionnement de la capsule surrénale humaine dans les gangrènes gazeuses, Compt. rend. Soc. de biol. **81**:14, 1918.

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26. Albrecht, H., and Weltmann, O.: Ueber das Lipoid der Nebennierenrinde, Wien. klin. Wchnschr. **24**:483, 1911.

27. Hueck, E.: Ueber experimentell erzeugte Veränderungen im Lipoidgehalt der Nebennierenrinde und ihre Beziehungen zum Cholesteringehalt des Blutes, Verhandl. d. deutsch. path. Gesellsch. **15**:251, 1912.

28. Wülfing, M.: Die Veränderungen der Nebennierenrinde bei Infektionskrankheiten, Virchows Arch. f. path. Anat. **253**:239, 1924.

the average weight is 13.4 Gm. The more striking depletion of cortical lipoid is seen in cases of acute infectious diseases of the most fulminating type (fig. *E*).

Infectious diseases are not the only conditions in which such changes in the adrenal glands are known to occur. They have been described by Landau,[15] Albrecht and Weltmann [26] and Hueck [27] in various neoplastic diseases. Ball and Samuels [29] demonstrated adrenal enlargement in animals with experimentally produced tumors. These authors suggested that the enlargement might in some way be attributed to the extreme breakdown of necrotic tumor tissue. In the present series it is apparent that while cancer per se is associated with slight enlargement of the adrenal glands without significant alteration in the cortical lipoid content, the more striking adrenal enlargement associated with marked depletion of lipoid is found in those cases of cancer which are complicated by cachexia.

In addition to infectious diseases and malnutrition with their attendant metabolic disorders, other pathologic conditions may be associated with adrenal enlargement and depletion of lipoid. The latter include pemphigus, eczema, extensive burns and protracted vomiting. It can be seem that all of these conditions, associated with marked dehydration and depletion of chlorides, throw an increased demand on the adrenal glands. Illustrative examples follow.

A 79 year old man had had acute pemphigus for four months. The skin and the mucous membranes were the site of most extensive denudations. A terminal rise in the blood nonprotein nitrogen occurred. The adrenal glands together weighed 15.80 Gm. and the widened cortex exhibited marked depletion of lipoid. Adrenal changes like those just described have been observed in man after extensive burns (Kolosko,[30] Napp,[31] Albrecht and Weltmann [26]) and have been experimentally reproduced by Pfeiffer,[32] Nakata [33] and Niemeyer.[34] Kamniker [35] noted similar changes in a child dying with extensive eczema.

Protracted vomiting was the chief symptom in the next case. The patient was a 58 year old woman suffering from high intestinal obstruction. After four days of persistent emesis, she was admitted to the hospital in profound shock associated with dehydration. She died twelve hours after admission. Her adrenal glands weighed 17.12 Gm., and the widened cortex showed depletion of lipoid.

Similar changes were observed by Wohl and his co-workers [36] following experimental high intestinal obstruction. Treatment with large amounts of extract of adrenal cortex was found by these authors to prolong markedly the period of survival after experimental ligation of the jejunum.[37] Scudder and his associates [38] reported elevation of serum potassium in experimental intestinal obstruction.

29. Ball, H. A., and Samuels, L. T.: Adrenal Weights in Tumor-Bearing Rats, Proc. Soc. Exper. Biol. & Med. **38**:441, 1938.

30. Kolosko, A.: Ueber Befunde an den Nebennieren bei Verbrennungstod, Vrtljschr. f. gerichtl. Med. (supp. 1) **47**:217, 1914.

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34. Niemeyer, R.: Ueber Nebennierenveränderungen bei experimentellen Vergiftungen und bei Verbrühungen, Ztschr. f. d. ges. exper. Med. **14**:346, 1921.

35. Kamniker, K.: Beitrag zur Kenntnis der Nebennierenblutungen, Frankfurt. Ztschr. f. Path. **35**:487, 1927.

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37. Wohl, M. G.; Burns, J. A., and Pfeiffer, G.: High Intestinal Obstruction in the Dog Treated with Extract of Adrenal Cortex, Proc. Soc. Exper. Biol. & Med. **36**:549, 1937.

38. Scudder, J.; Zwemer, R. L., and Truszkowski, R.: Potassium in Acute Intestinal Obstruction, Surgery **1**:74, 1937.

The conclusions concerning the mutual relations of the adrenal cortex and systemic disease are fragmentary and require further documentation. This is illustrated by another case:

A 65 year old woman, known to be addicted to the use of alcoholic beverages, suffered from persistent emesis for several months prior to death. On admission to the hospital she was semicomatose, with a blood pressure of 50 systolic. The diastolic pressure was not obtainable. She presented all the signs of peripheral circulatory collapse. The nonprotein nitrogen of the blood amounted to 56 mg. per hundred cubic centimeters, and the chlorides were markedly depressed to the level of 60 milliequivalents. Despite the administration of blood and saline solution, she never recovered from shock, dying in forty-eight hours. At autopsy no cause of death could be demonstrated. It was generally agreed that the electrolyte disturbance was responsible for her death. The adrenal glands were enlarged, weighing 16.35 Gm. In contrast with the adrenal cortex in the first cited case of vomiting, the cortex in this instance contained abundant lipoid.

It should be emphasized that all of the aforementioned conditions, including infectious diseases, pemphigus, eczema, burns and protracted vomiting, are associated with signs and symptoms of adrenal insufficiency of varying degree. Moreover, death in the conditions enumerated may at times be attributed to adrenal insufficiency. The lowering of blood chlorides in infectious disease is well known (Peters and Van Slyke [39]). Changes in the electrolyte pattern of the blood characteristic of adrenal insufficiency have been described by Talbot and his co-workers [40] in pemphigus and by Stoesser [41] in infantile eczema. Talbot stated that administration of large amounts of extract of adrenal cortex resulted in correction of the electrolyte disturbance and simultaneous clinical improvement. Maclean,[42] Nitschke and Krätschell [43] and Stenger [44] found elevation of serum potassium and depression of serum chlorides, associated with hemoconcentration, in cases of severe burns and infectious diseases.

As can be seen from the foregoing citations, the literature contains extensive reference to the pathologic alteration of the adrenal glands. The emphasis, however, has been on the direct effect of various pathologic conditions on these glands. The changes secondary to metabolic disturbances associated with disease have not been adequately considered.

The adrenal glands are recognized by all to be intimately concerned with water, electrolyte, protein and carbohydrate metabolism. Recent papers point to the important role of these glands in protein metabolism. Long and his co-workers [45] demonstrated that adrenocortical compounds furthered the conversion of body protein to carbohydrate. It has been shown recently by Levin and Leathem [46] that the decrease in serum albumin following hypophysectomy may be corrected by administration of desoxycorticosterone acetate. Adrenal hypertrophy has been

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40. Talbot, J. H.; Lever, W. F., and Consolazio, W. B.: Metabolic Studies on Patients with Pemphigus, J. Invest. Dermat. **3**:31, 1940.

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44. Stenger, K.: Blutveränderungen bei schweren Infektionskrankheiten und bei Verbrennungen. Ihre Beziehung zur Nebennierenschädigung, Klin. Wchnschr. **18**:576, 1939.

45. Long, C. N. H.; Katzin, B., and Fry, E. G.: Adrenal Cortex and Carbohydrate Metabolism, Endocrinology **26**:309, 1940.

46. Levin, L., and Leathem, J. H.: The Relation of the Pituitary, Thyroid and Adrenal Glands to the Maintenance of Normal Serum Albumin and Globulin Levels, Am. J. Physiol. **136**:306, 1942.

observed following acute starvation (Jackson [47]; Mulinos and Pomerantz [48]; Sarason [49]) as well as the feeding of a diet rich in protein (Engel and Tepperman [50]; Sarason [49]). Whitehead [51] described cortical proliferation in the adrenal glands of mice after injections of peptone. These are all instances of accelerated protein catabolism. The marked adrenal enlargement associated with depletion of lipoid in cachectic patients may be explained on the basis of increased breakdown of body protein. Engel and Tepperman [50] stated that an increase in protein catabolism is often the underlying factor in various diverse conditions known to be associated with adrenal hypertrophy. Coincident with this accelerated breakdown of tissue protein there is liberation of intracellular potassium. It seems not unlikely, therefore, that the adrenal changes observed in those clinical conditions associated with profound disturbances of electrolyte and protein metabolism are the manifestations of increased demands made on the adrenal cortex.

While this paper serves to emphasize changes of the adrenal cortex secondary to metabolic disturbances associated with systemic disease, it must not be forgotten that the disease itself may directly involve the adrenal glands giving rise to symptoms of adrenal insufficiency. Hemorrhage, infarction and necrosis of the adrenal gland occurring in the course of severe infectious diseases have been emphasized by Thomas,[21] Oberndorfer,[52] Hutinel,[53] Fraenkel,[20] Kovacs,[54] Furuta,[55] Simmonds,[56] Goldzieher [57] and others. In the present series they were not a prominent feature and did not exceed an occasional focal miliary extravasation of red blood cells. Mention should be made, however, of the case of a 61 year old man who, two hours after an injection of bromsulfalein, showed a rise in temperature and signs and symptoms of shock. (The dye used was from a lot which has caused marked febrile reactions in other patients.) The state of shock terminated in death after eighteen hours. The autopsy disclosed massive bilateral adrenal hemorrhages with necrosis of cortex and medulla associated with thrombus formation in the large veins. No inflammatory disease was found anywhere in the body. This is in contrast to the so-called Waterhouse-Friederichsen syndrome, which consists of bilateral hemorrhagic infarction of the adrenals associated with septicemia, particularly meningococcemia. Virchow [58] mentioned 2 cases of sudden death of previously healthy persons in which the only pathologic change was hemorrhagic infarction of the adrenal glands.

47. Jackson, C. M.: Effects of Acute and Chronic Inanition upon the Relative Weights of the Various Organs and Systems of Adult Albino Rats, Am. J. Anat. **18**:15, 1915.

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57. Goldzieher, M.: The Adrenals, New York, The Macmillan Company, 1929.

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Josué,[59] Landau,[15] Albrecht and Weltmann,[26] Hueck [27] and Thomas [60] described adrenal enlargement with increased storage of lipoid in contracted kidneys. The marked increase in the weight of the adrenal glands associated with lipoid storage in nephrosclerosis (average weight, 15.9 Gm.) and the less marked enlargement in hypertension following chronic glomerulonephritis and pyelonephritis (average weight, 13.5 Gm.) are difficult to explain. These findings corroborate those recently reported by Rinehart and his co-workers [61] in similar cases of hypertension. The latter authors suggested "hypersecretion of the adrenal cortex may in some cases be a factor in the genesis of what is now classified as essential hypertension."

The enlargement of the adrenal glands in hypertension is in contrast to the normal weight (average, 11.6 Gm.) and normal histologic appearance of the glands in atherosclerosis of the large arteries. These findings conflict with those reported by Hueck [27] and others.

Leibegott [18] and more recently Durlacher [62] demonstrated increased storage of glycogen in the myocardium of infants dying with erythroblastosis foetalis. Quantitative chemical analysis (Durlacher) and Best's carmine stain have been employed to show the increase in cardiac glycogen. The disturbance in carbohydrate metabolism in erythroblastosis is very likely correlated with the striking adrenal enlargement. Whether the latter is the result of the faulty carbohydrate metabolism or the primary cause remains to be settled.

SUMMARY

The adrenal glands of 110 patients were studied in an effort to correlate cortical changes with systemic disease.

Cortical enlargement associated with depletion of lipoid or reversal of lipoid pattern was found associated with inflammatory diseases, cachexia, pemphigus and protracted emesis.

Cortical enlargement with an increased amount of lipoid was encountered in cases of hypertension; the change was more striking when the hypertension was associated with primary vascular disease. The explanation of these changes is not at hand.

No significant alterations were present in the series of cases of atherosclerosis.

Extreme enlargement was found in 4 cases of erythroblastosis foetalis.

This study serves to emphasize that the enlargement of the adrenal cortex and the depletion of lipoid are reflections of the metabolic disturbances associated with certain systemic diseases and not the direct effect of the latter.

Dr. Rolf Katzenstein aided in the preparation of this article and in the compilation of the bibliography. Miss Virginia Lane and Mr. Luther Mardiros gave technical assistance.

New Haven Hospital.

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Progress in Internal Medicine

DISEASES OF THE HEART

A REVIEW OF SIGNIFICANT CONTRIBUTIONS MADE DURING 1942

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ANATOMY, PHYSIOLOGY AND METHODS

Beginning with the thesis that there must be full agreement between the structure and the function of the heart, Robb and Robb [1] have briefly, yet cogently, correlated the results of certain anatomic and physiologic studies. They point out that anatomists have repeatedly demonstrated that the ventricles of mammalian hearts are made up of discrete muscle bands and that the origin, the course and the attachments of these separate muscles are also fairly well known. These views, however, are not compatible with the assumption, held by many investigators, that the whole heart is one syncytium. If this were absolutely true, the Robbs point out, the findings of the anatomists would have to be considered artefacts. Further proof of the view that the cardiac musculature is indeed composed of distinct muscles is seen in (1) the specific functions of the several ventricular muscles, (2) the individual blood supply of each and (3) the fact that injury may be localized to a particular muscle and that such injury produces a constant and characteristic change in the electrocardiograms of various animals. Further proof is looked for from work in progress designed to show (1) whether the sheaths surrounding the muscle bands extend throughout their course, and (2) whether there are in fact specialized conduction pathways with a distribution similar to that of the Purkinje tissue in ungulates.

Richards and his associates [2] found that the average right auricular pressure in 6 normal human subjects was plus 37 mm. of water. Direct measurements of venous pressure were made by introducing a catheter into the right auricle and locating the position of the tip by means of roentgen rays. Their findings are of particular interest because it has long been assumed (on the basis of experiments in animals) that the average right auricular pressure is zero or slightly less. Richards and associates further found that the average gradient from arm to heart was plus 41 mm. of water in normal subjects, whereas in 3 patients with congestive heart failure the pressures in the vein of the arm and the right auricle were almost the same.

Cournand, Ranges and Riley [3] have tested the accuracy of the ballistographic method of determining cardiac output by comparing it with a method (involving

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The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the United States Navy Department.

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catheterization of the right auricle) based on the Fick principle. They found that with the latter method the cardiac output was 18.5 per cent greater than the value calculated from the ballistocardiogram with Bazett's tables for the internal cross section of the aorta. However, when diodrast was used for visualization in determining aortic cross section, the two methods checked very closely, the average difference being 3.5 per cent. They suggest, therefore, that with respect to absolute accuracy the ballistocardiographic method may be improved either by making a correction of 18.5 per cent or by using diodrast in the determination of the aortic cross section.

Rappaport and Sprague [4] have discussed in a comprehensive manner the graphic registration and interpretation of normal heart sounds. They point out that an observer using an ordinary stethoscope does not hear the cardiac sound vibrations as they actually are because of three major forms of distortion:

1. The heart sounds are modified in their path of travel from the source to the surface of the chest.

2. The vibrations that reach the surface of the chest are further modified by the stethoscope and type of chest piece employed.

3. The human hearing mechanism (that is, the ear, the nervous pathways, and the brain) additionally modifies the heart sound vibrations.

Phonocardiographic registration may also be considered in the light of the same modifications or distortions, with the types being defined as follows:

a. Linear phonocardiography, or the registration of the sound vibrations as they exist on the surface of the chest.

b. Stethoscopic phonocardiography, or the registration of the sound vibrations as they are transmitted to the ears by an average acoustic stethoscope.

c. Logarithmic (human audiographic) phonocardiography, or the registration of sound vibrations as they are perceived by a competent observer if the personal factors are omitted.

The advantages of each type in the analysis of the heart sounds are clearly outlined, as well as the advantages of a simultaneous recording of the venous pulse.

Their observations indicate that the first heart sound comprises four components, the second and third of which are ordinarily heard in auscultation:

a. The first, which is caused by residual vibrations of auricular origin.

b. The second, which is produced at the beginning of the isometric contraction phase of the cardiac cycle (closure of the mitral and tricuspid valves).

c. The third, which is caused by the opening of the semilunar valves.

d. The fourth, which is caused by the acceleration of the blood in the arterial vessels during the maximum ejection phase of ventricular systole.

The second heart sound also comprises four components, of which only the second is heard in auscultation:

a. The first vibrations, which represent the beginning of the diastolic fall in pressure with ventricular relaxation.

b. The second group of vibrations, which are caused by the closure of the semilunar valves (termination of ventricular systole).

c. The third group, which are most likely due to the arterial wall and blood column vibrations. An additional possible source of vibration in this phase of the second heart sound may be the natural period vibration of the chest wall, which may conceivably be set into oscillation by the second component.

d. The fourth component is caused by the opening of the mitral and tricuspid valves.

4. Rappaport, M. B., and Sprague, H. B.: The Graphic Registration of the Normal Heart Sounds, Am. Heart J. **23**:591, 1942.

An impressive normal sinoauricular bradycardia has been reported by White [4a] in 4 athletes, 3 of whom were long distance runners. The basal heart rates in the 4 athletes were as follows: a marathon winner, 38; an aviator, 38; a champion miler, 37, and a champion two-miler, 35. Thus, the range of the normal heart rate has been shown to be more extended than previously thought.

CARDIAC ARRHYTHMIAS

Wolff [5] has discussed the paroxysmal tachycardias primarily from the standpoint of the clinical manifestations. His series of 125 cases included 81 instances of paroxysmal auricular fibrillation, 24 of paroxysmal auricular tachycardia, 11 of paroxysmal auricular flutter and 9 of paroxysmal ventricular tachycardia. Various types of heart disease were represented in varying grades of severity. There were, in addition, 25 instances in which the heart was normal. Wolff found that the significant variables include the ventricular rate (and in a lesser degree the type of rhythm), the underlying heart disease, the cardiac reserve, the sensitiveness of the patient and the presence or the absence of embolism. A ventricular rate of 150 a minute was found to be critical; below this rate symptoms are not often provoked unless embolism complicates the paroxysm, whereas at rates above 150 symptoms are usually induced regardless of all other variables. The type of rhythm is significant chiefly because of the association of different types with certain forms of heart disease. The nature and the severity of the underlying heart disease have an important influence on the symptoms. Patients with mitral stenosis in whom a paroxysm of rapid tachycardia develops become dyspneic, and pulmonary edema and hemoptysis may occur. Patients who experience angina on effort suffer similarly during paroxysms unless the rate is under 150. In patients with congestive failure or greatly limited cardiac reserve the onset of a paroxysm, especially if rapid and prolonged, may precipitate gross congestive failure. Even here, however, the heart rate is a critical factor, because at rates much below 150 no aggravation of signs or symptoms is noted. Wolff agrees that heart failure may occur in persons with normal hearts as a result of a paroxysm of rapid tachycardia but hints that this is not common save in infants and children. In 41 of Wolff's 125 cases symptoms were not provoked; all types of tachycardia were represented as well as various types and stages of heart disease.

Cooke and White [5a] have published a study of paroxysmal tachycardia and paroxysmal auricular fibrillation, consisting of an analysis of 750 cases encountered in the cardiographic laboratory at the Massachusetts General Hospital from 1928 to 1938. They concluded that when the cardiovascular system is normal, attacks of paroxysmal tachycardia are uncomfortable but relatively unimportant incidents, without effect on longevity, but that the occurrence of an attack in a patient seriously ill must be regarded with apprehension, and the occurrence of heart failure as the result of an attack may lead to the formation of intracardiac thrombi and subsequent emboli.

In a second paper [5b] these same authors discussed 27 cases of ventricular paroxysmal tachycardia, 24 of which were found in a review of electrocardiograms

4a. White, P. D.: Bradycardia (Below Rate of 40) in Athletes, Especially in Long Distance Runners, Correspondence, J. A. M. A. **120**:642 (Oct. 24) 1942.

5. Wolff, L.: Clinical Aspects of Paroxysmal Rapid Heart Action, New England J. Med. **226**:640, 1942.

5a. Cooke, W. T., and White, P. D.: Prognosis of Paroxysmal Tachycardia and Paroxysmal Auricular Fibrillation, Brit. Heart J. **4**:153, 1942.

5b. Cooke, W. T., and White, P. D.: Paroxysmal Ventricular Tachycardia, Brit. Heart J. **5**:33, 1943.

taken on 25,000 patients in the cardiographic laboratory of the Massachusetts General Hospital from 1914 to 1929. They established the following four criteria for diagnosis.

1. The presence of P waves at a slower rate than that of abnormal QRS waves during a paroxysm of tachycardia.
2. A paroxysm of abnormal ventricular complexes, i. e., three or more, occurring during auricular fibrillation.
3. The onset of tachycardia with an abnormal ventricular complex.
4. Close resemblance of the complexes of ventricular premature beats to the complexes occurring during paroxysmal tachycardia.

Coronary heart disease was present in 22 of the 27 cases; in 4 other cases the heart was apparently normal, and in 1 it was thought to have a congenital ventricular defect. There were 17 males and 10 females, the youngest being aged 18 years and the oldest 81 years. Digitalis had been administered to 13 of the 27 patients before the onset of the tachycardia and was probably the chief etiologic factor in at least 5 of them. The prognosis was generally but not always poor. Only 2 patients with coronary heart disease survived longer than two years after the first attack; 5 patients with hearts otherwise normal had survived to the date of writing, the periods varying from two to fifteen years.

Rosenbaum, Johnston and Keller [6] have described in detail their findings in 2 cases of paroxysmal ventricular tachycardia in childhood and have briefly summarized the 7 other definite cases previously reported. In 3 of the 9 cases there was no associated cardiac abnormality, while in the remaining 6 there was congenital or acquired heart disease. In 7 of the 9 cases there were important symptoms associated with the paroxysms (slowest ventricular rate, 192), including abdominal pain, dyspnea, nausea and vomiting, anorexia and pain in the chest. In 1 case there were no associated symptoms, but the paroxysms were short, and in the remaining case there were repeated bouts of fever associated with the tachycardia. The authors stress the importance of accurate diagnosis and the value of adequate doses of quinidine sulfate in restoring normal rhythm.

Ungerleider and Gubner [7] have written an interesting report of their observations on premature beats and the mechanism of palpitation. Electrocardiograms were obtained on 1,142 applicants for life insurance who were found to have premature beats on clinical examination; in 58 per cent there was no evidence of heart disease. Among the factors which were found to increase the significance of premature beats were:

1. The occurrence of premature beats of multifocal origin.
2. Frequent and persistent premature beats, particularly if they occur successively in short runs interrupting the regular rhythm.
3. A definite increase in the number or shower of extrasystoles immediately following exercise.
4. Occurrence of premature contractions in the presence of a rapid heart rate.
5. Inversion of the T wave in the regular beat which follows the extrasystole.
6. Post-extrasystolic pulsus alternans.

The last-named factor refers to the occurrence of temporary pulsus alternans following the premature beat, which is probably due to left ventricular strain. This was observed in 21 of 42 cases of heart disease, "and the degree of alternation

6. Rosenbaum, F. F.; Johnston, F. D., and Keller, A. P.: Paroxysmal Ventricular Tachycardia in Childhood, Am. J. Dis. Child. **64**:1030 (Dec.) 1942.

7. Ungerleider, H. E., and Gubner, R.: Extrasystoles and the Mechanism of Palpitation. Tr. Am. Therap. Soc. **41**:1, 1942.

paralleled the gravity of the cardiac lesion." In a group of 97 normal subjects with premature beats, on the other hand, alternation for more than three beats following the premature beat "was never observed, except for transitory and minimal alternation in 3 subjects with tachycardia." The authors present their evidence that palpitation occurring with premature beats is not due to the extra large beat which follows but to the premature beat itself. They point out that when the onset of ventricular systole occurs prematurely and at a time when rapid diastolic inflow is still continuing and the auriculoventricular valves are widely separated, the cusps are brought together more forcibly than normal so that the intensity of the first sound is increased, and that with this there may be consciousness of the heart beat.

Perera, Levine and Erlanger,[8] prompted by the clinical impression that patients with bundle branch block of the right type have a better prognosis than do those with the left type, were able to confirm this impression by an analysis of 104 cases of right bundle branch block. They found that the average survival time after the diagnosis of right bundle branch block was three years for 29 patients who died and four years and one month for 62 patients remaining alive. Thirteen patients could not be traced. They found that the prognosis for life was one year and two months for 60 patients with left bundle branch block, which is in accord with the experience of most other investigators.

White and Blumgart [9] have reported 2 cases which are of considerable interest in the further appraisal of the use of quinidine in the treatment of certain cardiac arrhythmias. They point out that although the appearance of embolic phenomena during the course of auricular fibrillation is generally regarded as a contraindication to the use of quinidine, yet in certain cases, as exemplified in a patient of theirs, the restoration of normal rhythm may result in the cessation of embolism. A further example is given of the use of quinidine in restoring normal rhythm in a patient with active rheumatic infection, congestive failure and auricular fibrillation in whom digitalis failed to control adequately the ventricular rate. The use of quinidine, ordinarily thought to be contraindicated in the presence of rheumatic fever and congestive failure, was considered to be life saving.

ELECTROCARDIOGRAPHY

Genesis of the Electrocardiogram.—During the past few years there has accumulated an impressive body of knowledge serving to cast doubt on the validity of Einthoven's equilateral triangle hypothesis. These investigations and the controversies surrounding them have been of small concern to those primarily interested in clinical electrocardiography, since Einthoven's hypothesis seemed to serve for all practical purposes. However, the recent work of Wolferth, Livezey and Wood [10] stands in contradiction to this hypothesis and, more important, the methods used point the way to possible new advantages of a clinical nature.

They have shown that the pattern of potential variations along radial lines extending, roughly, from the heart to the tip of each shoulder, does not change significantly except for decrement as the distance from the heart increases. By pairing appropriate areas along these lines they obtained a series of tracings closely resembling lead 1. On the right side the deflections ("C-1 pattern") were relatively large near the heart in the C_1 area (fourth intercostal space to the right of

8. Perera, G. A.; Levine, S. A., and Erlanger, H.: Prognosis of Right Bundle Branch Block, Brit. Heart J. **4**:35, 1942.

9. White, P. D., and Blumgart, H. L.: Cessation of Repeated Pulmonary Infarction and of Congestive Failure After Termination of Auricular Fibrillation by Quinidine Therapy, J. Mt. Sinai Hosp. **8**:1095, 1942.

10. Wolferth, C. C.; Livezey, M. M., and Wood, F. C.: Studies on the Distribution of Potential Concerned in the Formation of Electrocardiograms, Am. J. M. Sc. **203**:641, 1942.

the sternum) but became progressively smaller as the tip of the shoulder was approached. On the left side the deflections ("C-5 pattern") were relatively large near the heart in the C_5 area (fifth intercostal space in the left anterior axillary line) but became smaller as the left shoulder tip was approached. Because lead 1 represents the subtraction of the C_1 from the C_5 pattern, which are chiefly derived from different parts of the heart, and after each has undergone decrement, it seems reasonable to suppose that the study of the C_1 and C_5 patterns separately should prove valuable. Wolferth and his associates admittedly have made only a beginning with this new method, but its possible advantages seem very important.

Nahum, Hoff and Kaufman [11b] have now reported observations on the nature of the Q and S waves. These observations form part of a more extended work, previously reported,[12] on the genesis of the normal and of the abnormal electrocardiogram in experimental animals. They found that the downstroke of Q_1 is produced by early electrical activity in the anterior surface of the left ventricle and the upstroke by electrical activity in the posterior surface of the right ventricle, while the downstroke of Q_3 is produced by early electrical activity in the posterior surface of the left ventricle and the upstroke by excitation of the anterior surface of the right ventricle. The downstroke of S_3 develops with the complete activation of the posterior surface of the left ventricle while a portion of the anterior surface of the right ventricle is not yet active, and the upstroke of S_3 occurs when the remainder becomes active and restores isopotentiality. S_1 probably arises from a similar sequence of excitation in the anterior surface of the left and the posterior surface of the right ventricle. These findings are wholly in accord with their previous observations that lead 1 is formed by the summation of the anterior levocardiogram and the posterior dextrocardiogram and lead 3 by the summation of the anterior dextrocardiogram and posterior levocardiogram.

Fetal Electrocardiography.—The recording of the electrocardiogram of the fetus has passed from the stage of medical curiosity to that of practical clinical application. Recent studies [13] have shown that by the use of proper technics fetal electrocardiograms may be obtained from the fourth month until the end of pregnancy. The obtaining of records earlier in pregnancy, desirable though this may be, is not likely to prove successful because of the shielding effect of the membranes and the amniotic fluid. The percentage of positive results increases with the length of pregnancy, and in the last month failures are rare. The curves do not have the same configuration as those from adults, and interpretation is made still more difficult because of artefacts. Nevertheless a number of measurements can be made. Fetal hearts generally show sinus arrhythmia and may show extrasystoles and varying degrees of heart block. There is little change in the fetal heart rate from the fourth month to the end of pregnancy, and there is no correlation between the fetal heart rate and the maternal heart rate or the sex of the fetus. This method is useful in the clinical study of effects of various drugs and procedures on the fetal heart.

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11. (*a*) Hoff, H. E.; Nahum, L. H., and Kaufman, W.: The Nature of Q-1 and Q-3, Am. J. Physiol. **135**:752, 1942. (*b*) Nahum, L. H.; Hoff, H. E., and Kaufman, W.: The Nature of the S Complex of the Electrocardiogram, ibid. **136**:726, 1942.

12. Graybiel, A., and White, P. D.: Diseases of the Heart: A Review of Significant Contributions Made During 1941, Arch. Int. Med. **70**:303 (Aug.) 1942.

13. (*a*) Goodyer, A. V. N.; Geiger, A. J., and Monroe, W. M.: Clinical Fetal Electrocardiography, Yale J. Biol. & Med. **15**:2, 1942. (*b*) Bernstein, P., and Mann, H.: A Clinical Evaluation of Fetal Electrocardiography, Am. J. Obst. & Gynec. **43**:21, 1942. (*c*) Mann, H., and Mayer, M. D.: The Uterine Electrocardiogram, J. Mt. Sinai Hosp. **8**:805, 1942. (*d*) Ward, J. W., and Kennedy, J. A.: The Recording of the Fetal Electrocardiogram, Am. Heart J. **23**:64, 1942.

Influence of Posture, Drugs, Exercise and Other Factors on the Electrocardiogram.—White and his colleagues [13e] have reported the finding of an inversion of the T waves in lead 2 of the electrocardiogram as a normal physiologic variation in occasional persons, particularly those of asthenic habitus with vertical hearts and with a tendency toward neurocirculatory asthenia. The position of the heart was the most important factor in producing this inversion of the T waves, which was found in the sitting or the standing position and was corrected by recumbency or by an elevation of the diaphragm such as that at full expiration. Autonomic nervous influences comprise another factor, less striking as a rule. The relatively common normal occurrence of inversion of the T waves in lead 2 makes imperative that one recognize it in order to avoid an erroneous diagnosis of heart disease.

Mayerson and Davis [14] have described the changes in the electrocardiogram of a normal subject when the latter is passively tilted from the horizontal to the upright (75 degree) position. They believe the initial changes are due to a shift in the position of the heart and to alterations in its contact with neighboring tissues but that the later changes are due primarily to increased sympathetic activity occasioned by the decreased venous return and consequent relative cerebral anoxia. Mayerson and Davis do not believe the electrocardiographic changes they observed are due to anoxemia of the myocardium as do some authors. The outstanding changes observed were an increase in the amplitude of P in leads 2 and 3, a decrease in the amplitude of T in all leads, a shift of the average QRS axis to the right and of the average T axis to the left, and a decrease in the QRST area. Stewart and Bailey [15] have described the variations in the form of the chest leads with change in position and found that as the subject's posture was changed from supine to sitting, to lying on the left side, the outstanding changes consisted of a decrease in the amplitude of the R and T waves, which varied concordantly, and in many cases a decrease in the amplitude of the S waves.

Hartwell and his associates [16] found that exercise, epinephrine, atropine and acetylbetamethylcholine chloride (mecholyl chloride) all had a tendency to lower the T waves of the electrocardiogram, while ergotamine increased the amplitude of T. Pettus and his co-workers [17] found no characteristic changes in electrocardiograms following the administration of large doses of morphine to normal subjects and to patients with heart disease. Geiger and his collaborators [18] found that a significant lowering or inversion of the T waves of the electrocardiogram occurred during or shortly after massive arsenotherapy, with a return to the normal within a few weeks. Stewart and Smith [19] observed various arrhythmias and changes in the T waves and RST segments as a result of the administration of potassium salts.

13e. White, P. D.; Chamberlain, F. L., and Graybiel, A.: Inversion of the T Waves in Lead II Caused by Variation in the Position of the Heart, Brit. Heart J. **3**:233, 1941.

14. Mayerson, H. S., and Davis, W. D., Jr.: The Influence of Posture on the Electrocardiogram, Am. Heart J. **24**:593, 1942.

15. Stewart, H. J., and Bailey, R. L.: The Effect of Posture on the Form of Precordial Leads of the Electrocardiogram, Am. Heart J. **18**:271, 1939.

16. Hartwell, A. S.; Burrett, J. B.; Graybiel, A., and White, P. D.: Effect of Exercise and of Four Commonly Used Drugs on Normal Human Electrocardiogram, with Particular Reference to T Wave Changes, J. Clin. Investigation **21**:409, 1942.

17. Pettus, W. W.; Geiger, A. J., and Grzebien, T.: Effects of Morphine on the Electrocardiogram of Man, Yale J. Biol. & Med. **14**:493, 1942.

18. Geiger, A. J.; Craige, B., Jr., and Sadusk, J. F., Jr.: Observations on the Massive Dose Arseno-Therapy of Early Syphilis by the Intravenous Drip Method: II. Electrocardiographic Abnormalities Associated with Massive Arsenotherapy, Yale J. Biol. & Med. **14**:357, 1942.

19. Stewart, H. J., and Smith, J. J.: Changes in the Electro-Cardiogram and in the Cardiac Rhythm During the Therapeutic Use of Potassium Salts, Am. J. M. Sc. **201**:177, 1941.

CARDIOVASCULAR ROENTGENOLOGY

Comeau and White [19a] have made a critical analysis of the standard methods of estimating the size of the heart from roentgen measurements. Their most important conclusion is that the range of size of the normal heart is great and has not yet been adequately determined in roentgen studies. More suitable standards for comparison with the area of the roentgen heart shadow than height, weight and body surface are needed, and probably measurements of body build of one kind or another will eventually help to solve the problem. The authors state that a comparison of the transverse diameters, the frontal areas and the volumes of 200 normal hearts (150 from males and 50 from females) leads one to conclude that the transverse diameter of the heart compares favorably with the other actual cardiac measurements and is the most satisfactory from the clinical standpoint. The application of cardiac transverse diameters to prediction tables by the use of the Hodges-Eyster figures is recommended with a view to discarding the other measurements, such as the cardiothoracic ratio. The measurement of the frontal area, although fairly satisfactory, was found less suitable, since it is not so completely an objective measurement. Prediction tables for the transverse diameter based both on orthodiographic and teleoroentgenographic measurements are now available.

CONGENITAL HEART DISEASE

Gelfman and Levine [20] have determined the incidence of bacterial endocarditis and endarteritis in cases of congenital heart disease based on an analysis of 34,023 autopsy protocols in four large hospitals of Boston. There were 453 cases (1.3 per cent) of congenital heart disease, of which 6.6 per cent showed superimposed bacterial infection. However, 272 (60 per cent) of the 453 congenitally abnormal hearts were from patients who died before the age of 2 years, and a complicating cardiac bacterial infection had developed in only 5 of these. The incidence of bacterial endocarditis in the remaining 181 cases was found to be 16.6 per cent, and these cases are separately considered as follows: Bacterial infection was not present in any cases of interauricular septal defect but was present in 42 per cent of all and 57 per cent of the uncomplicated cases of interventricular septal defect; in 28 per cent of all and 20 per cent of the uncomplicated cases of patent ductus arteriosus; in 21.2 per cent of cases of bicuspid aortic valves; in 29 per cent of cases of pulmonary stenosis and in 28.6 per cent of cases of the tetralogy of Fallot. It is of interest that 25 of the 181 cases of congenital defect were complicated by rheumatic infection, and subacute bacterial endocarditis was present in 8 of these 25 and was solely on the site of the rheumatic lesion in 5.

Mendelson and Pardee [21] have reported their experience with 20 pregnant patients who had congenital heart disease. The 20 cases formed 1.89 per cent of 1,089 instances of organic heart disease in approximately 31,000 obstetric cases. The particular defects in these cases were labeled as follows: pulmonary stenosis in 8 cases, interventricular septal defect in 4, coarctation of the aorta in 3, patent ductus arteriosus in 2, patent foramen ovale in 1, congenital defect, unclassified, in 2. Only 1 patient had congestive failure during pregnancy; the remaining 19 did not appear to suffer any ill effects. From a review of the previously reported cases as well as their own, Mendelson and Pardee conclude that

19a. Comeau, W. J., and White, P. D.: A Critical Analysis of Standard Methods of Estimating Heart Size from Roentgen Measurements, Am. J. Roentgenol. **47**:665, 1942.

20. Gelfman, R., and Levine, S. A.: The Incidence of Subacute Bacterial Endocarditis in Congenital Heart Disease, Am. J. M. Sc. **204**:324, 1942.

21. Mendelson, C. L., and Pardee, D. E. B.: Congenital Heart Disease During Pregnancy, Am. J. M. Sc. **202**:392, 1941.

patients with congenital heart disease should be evaluated in much the same fashion as other cardiac patients so far as pregnancy is concerned. To this general rule they make two exceptions: (1) Pregnancy in patients with coarctation of the aorta is attended by so great a risk that it should be avoided or interrupted, and (2) special precautions should be taken with patients in whom there exists the possibility of a reversal of an arteriovenous shunting of blood.

Prinzmetal [22] has described an ingenious method for determining whether or not a venous-arterial shunt is present in patients with congenital heart disease and the approximate magnitude of the shunt. One-half cubic centimeter of a 50 per cent solution of ether is injected into the antecubital vein with a needle of large bore (14 to 16 gage), and the interval between the time of injection and the moment the patient feels a prickly burning sensation in the face is recorded. In the absence of a venous-arterial shunt this facial sensation is not experienced because all the ether is eliminated by the lungs. In the event a shunt has been demonstrated, the observer injects a 50 per cent solution of saccharin, beginning with 0.1 cc. and successively increasing the dose by 0.1 cc. until the smallest amount which the patient can taste is determined. If 50 per cent or more of the circulating blood enters the shunt, the "saccharin time" will approximate the "ether time." If the former is considerably longer than the latter, it can be concluded that more than half of the blood goes through the regular channel, and the approximate percentage can be calculated as follows: Inject successively larger amounts of saccharin until the point is reached at which the circulation time suddenly becomes shorter. This indicates that the injection is large enough to permit a detectable quantity of saccharin to reach the tongue by way of the shunt. The approximate volume of the shunt (K) can be determined by means of the formula $K = \frac{a}{a\ c}$ in which a is the smallest amount of saccharin which can be tasted in the longer circulation period and c the smallest amount of saccharin that can be tasted in the shorter period.

Coarctation of the Aorta.—Stewart and Bailey [23] have reported their studies on 14 patients with coarctation of the aorta. The cardiac output was measured in 9 of the patients, and the output per square meter of body surface was found to be increased in 4 (2.85 to 3.45 liters), normal in 4 (1.93 to 2.10 liters) and decreased in 1 (1.61 liters). The basal metabolic rate was increased in 3 of the 9 patients, but the circulation time was not shortened as it is in patients with hyperthyroidism. The circulation time was within or near normal limits above the level of coarctation but was prolonged below this level in most instances. It is of interest that the most constant of the characteristic signs of coarctation was a higher systolic blood pressure in the arms than in the legs. The one exception to this rule was observed in a patient with only slight narrowing at the site of coarctation, whose condition was not diagnosed during life. Stewart and Bailey confirm the finding of Steele that the increase in peripheral resistance need not be confined to the upper half of the body but may be generalized and that under these circumstances so far as the distribution of peripheral arteriolar resistance is concerned, the arterial hypertension in coarctation of the aorta does not differ from the common forms of arterial hypertension.

Patent Ductus Arteriosus.—The cure of bacterial infection superimposed on patent ductus arteriosus represents a dramatic achievement. The results of Touroff

22. Prinzmetal, M.: Calculation of the Venous-Arterial Shunt in Congenital Heart Disease, J. Clin. Investigation **20**:705, 1941.

23. Stewart, H. J., and Bailey, R. L., Jr.: The Cardiac Output and Other Measurements of the Circulation in Coarctation of the Aorta, J. Clin. Investigation **20**:145, 1941.

and his associates [24] indicate that following the ligation of the ductus cure is the rule and failure to cure the exception. Similarly good results have been obtained by others who have followed Touroff's lead, and additional reports may be expected soon.

The extraordinary feature of this treatment is that simple ligation of the ductus should result in cure of the bacterial infection. The vegetations are rarely confined to the ductus, and even when they are, ligation or division of the ductus would not remove all of the vegetations or destroy all of the bacteria. Touroff,[24] in describing the effects of operation, speculates on this matter. He points out that after occlusion of the ductus healing of vegetations presumably occurs as a result either of the alteration of local mechanical factors or of changes in nutrition or of both. One theory is that the organisms die because they no longer enjoy the protection of the fibrin which was continuously precipitated by the action of swirling currents of blood. Another theory is that the growth of organisms in the ductus and the pulmonary artery is favored by the high oxygen content of the shunted blood and that an adequate supply of oxygen is lacking after the shunt it closed. It may be pointed out, however, that Streptococcus viridans infection may complicate other types of congenital defects in which the oxygen saturation of the arterial blood is low.

Further reports [25] on the operative cure of uncomplicated patent ductus arteriosus continue to show good results.

Interauricular Septal Defect.—Tinney and Barnes [26] have presented the findings in 4 additional cases of interauricular septal defect, 2 of which were complicated by mitral stenosis. One of the latter was further complicated by subacute bacterial endocarditis, and at necropsy a large vegetation was found directly in the interauricular septum. For some reason subacute bacterial endocarditis is an extraordinarily rare complication in cases of interauricular septal defect, this being the second recorded instance; even here the primary lesion may have been on the mitral valve, as this too was involved.

Uhley [27] has presented a new concept of the dynamics of interauricular septal defect based on a correlation between hydraulic principles and anatomic considerations. He criticizes the current view that preponderant dilatation and hypertrophy of the right ventricle and auricle are caused by shunting of blood through the communication, which in turn results from higher pressure in the left than in the right auricle. Uhley reviews the anatomic evidence showing that the auric-

24. (*a*) Touroff, A. S. W.: The Rationale of Operative Treatment of Subacute Bacterial Endarteritis Superimposed on Patent Ductus Arteriosus, Am. Heart J. **23**:847, 1942; (*b*) Blood Cultures from the Pulmonary Artery and Aorta in a Patient with Infected Patent Ductus Arteriosus, Proc. Soc. Exper. Biol. & Med. **49**:568, 1942. (*c*) Touroff, A. S. W., and Tuchman, L. E.: Subacute Streptococcus Viridans Endarteritis Superimposed on Patent Ductus Arteriosus. Spontaneous Recovery: Recurrence After Twelve Years; Recovery Following Surgical Treatment, Am. Heart J. **23**:857, 1942. (*d*) Touroff, A. S. W.; Vesell, H., and Chasnoff, J.: Operative Cure of Streptococcus Viridans Endarteritis Superimposed on Patent Ductus Arteriosus: Report of the Second Successful Case, J. A. M. A. **118**:890 (March 14) 1942.

25. Johnson, J.; Jeffers, W. A., and Margolies, A.: The Technique of the Ligation of the Patent Ductus Arteriosus, J. Thoracic Surg. **11**:347, 1942. Bourne, G.: Changes in Renal Function and Persistence of the Murmur After Ligation of Patent Ductus Arteriosus, Brit. Heart J. **3**:228, 1941. Dolley, F. S., and Jones, J. C.: The Surgical Treatment of Persistently Patent Ductus Arteriosus, Brunn, Med.-Surg. Tributes, 1942, p. 123. Nixon, J. W.: Ligation of the Patent Ductus Arteriosus: Successful Case, Surgery **12**:31, 1942.

26. Tinney, W. S., and Barnes, A. R.: Interauricular Septal Defect, Minnesota Med. **25**:637, 1942.

27. Uhley, M. H.: Lutembacher's Syndrome and a New Concept of the Dynamics of Interatrial Septal Defect, Am. Heart J. **24**:315, 1942.

ular axis is such that the left auricle occupies a definitely more cephalad position than the right. Further, the plane of the foramen ovale (septal defect) is almost horizontal, and not vertical as it is commonly represented. With the disposition of the chambers and the septal defect in this relation, filling of the right auricle is accomplished by the usual caval flow and by a gravitational flow through the communication in the floor of the superiorly placed left auricle. Dilatation of the right auricle results, and, in due time, the right side of the heart shows dilatation and hypertrophy, whereas the left auricle and ventricle, which play almost no role in these events, remain essentially unaffected. The aorta becomes hypoplastic because of the decreased systemic volume of blood. The pulmonary arterial tree, on the other hand, necessarily dilates to accommodate the increased volume of blood in the lesser circuit. The presence of mitral stenosis simply exaggerates the flow differences.

RHEUMATIC HEART DISEASE

The most important recent advance with respect to rheumatic heart disease is the piling up of evidence that recrudescences may be prevented by the use of one or other of the sulfonamide drugs. It may almost be stated as a fact that recurrences of rheumatic activity may be prevented in over 90 per cent of those so treated and that the natural history of the disease, as a consequence, may undergo a substantial change.

Kuttner and Reyersbach [28] have carried out a careful study, the results of which confirm the fact that streptococcic infections of the upper respiratory tract and rheumatic relapses in rheumatic children are prevented by the prophylactic administration of sulfanilamide. Their studies were carried out during two successive winters on rheumatic children living in an institution. There was every facility for daily clinical observation and routine bacteriologic studies.

The 108 rheumatic children were carefully divided into two groups matched as closely as possible with regard to age, sex, number of previous rheumatic attacks and cardiac findings. Beginning in October and continuing until the following June, those in one group received daily doses of sulfanilamide. During the first winter, 1 to 2 Gm. (depending on weight) was given in divided doses, and an average blood level of 2 mg. per hundred cubic centimeters was maintained. During the second winter the dose was slightly less, and the average blood level was 1.5 mg. per hundred cubic centimeters.

During the first winter 30 of the 54 children in the control group contracted pharyngitis due to group A hemolytic streptococcus type 15. Following a latent period varying from three to twenty-one days, 14 of these 30 had definite rheumatic recurrences, and an additional 4 had questionable recurrences. In contrast to this, only 1 child in the treated group contracted pharyngitis due to the type 15 streptococcus; the administration of the drug was continued, and no rheumatic sequelae developed.

During the second winter 17 children in the control group of 50 presented pharyngitis due to an unidentified type of group A hemolytic streptococcus. Following a latent period varying from ten to eighteen days, 9 of these 17 children had definite rheumatic recurrences and 1 a questionable recurrence. Only 1 child in the control group had pharyngitis due to the same organism and, following a latent period, mild rheumatic manifestations.

Toxic reactions developed in 15 per cent of the children receiving the drug; the others tolerated the drug well.

28. Kuttner, A., and Reyersbach: The Prevention of Upper Respiratory Infections and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide, J. Clin. Investigation **22**:77, 1943.

Kuttner and Reyersbach rightly point out that their results indicate not only the effectiveness of sulfanilamide in preventing streptococcic infections of the upper respiratory tract and recurrences of rheumatic fever but that infection with group A hemolytic streptococcus is an important factor in the etiology of rheumatic fever.

Hansen, Platou and Dwan [29] also obtained strikingly good results by administering sulfanilamide or, in a few instances, sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) or sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) to 53 children with rheumatic heart disease from October into June. Only 2 of the 53 treated children experienced a recurrence of rheumatic activity while of the 32 control children 17 experienced 21 recurrences, although there was no difference in the number of infections of the upper respiratory tract in the two groups. These results were in full accord with other clinical features which indicated that the treated group tended to be in better condition.

Coburn and Moore [30] have investigated the prophylactic value of salicylates in preventing rheumatic recurrences. Children with quiescent rheumatic heart disease were asked to report to the clinic at the onset of any attack of pharyngitis, at which time cultures of material from the throat were made, and a daily ration of 4 to 6 Gm. of salicylates was begun. If the cultures contained an organism other than group A hemolytic streptococcus, the treatment was discontinued and the patient omitted from the study. All but 1 of 47 patients treated with salicylates escaped clinical manifestations of rheumatic fever, while 57 of 139 controls suffered recurrences. The reviewers are not aware of any comparable study showing that the salicylates have any great value in preventing rheumatic recurrences. The advantages of their use, if confirmed, are obvious, especially the advantage that they may be successfully used during or immediately after the first phase (respiratory infection), at which time the sulfonamide compounds are not only valueless but contraindicated.

Wasson and Brown [31] have reported their further studies on immunization against rheumatic fever. Treatment consisted essentially in repeated injections of graduated doses of crude or modified hemolytic streptococcus toxin (N. Y. 5 strain). Patients so treated and followed over a period of years have had fewer recurrences than controls and, if their disease became active, had less severe symptoms. So far as prevention of recurrences is concerned, this method is more troublesome and the results not so good as when the sulfonamide compounds are given.

There have been a number of articles [32] dealing with various clinical phases of rheumatic fever which are of interest. Of especial importance is the report of Keith and Brick [32a] on the changes in the size of the heart with active rheumatic infection. In preparation for their work with patients suffering from rheumatic fever they observed the effect of rest in bed and of heart rate on normal controls.

29. Hansen, A. E.; Platou, R. V., and Dwan, P. F.: Prolonged Use of Sulfonamide Compound in Prevention of Rheumatic Recrudescences in Children: Evaluation Based on Four Year Study in Sixty-Four Children, Am. J. Dis. Child. **64**:963 (Dec.) 1942.

30. Coburn, A. F., and Moore, L. V.: Salicylate Prophylaxis in Rheumatic Fever, J. Pediat. **21**:180, 1942.

31. Wasson, V. P., and Brown, E. E.: Further Studies on Immunization Against Rheumatic Fever, Am. Heart J. **23**:291, 1942.

32. (*a*) Keith, J. D., and Brick, M.: Changes in the Size of the Heart in Children with Rheumatic Fever, Am. Heart J. **24**:289, 1942. (*b*) Levine, S. A., and Kauvar, A. J.: The Association of Angina Pectoris or Coronary Thrombosis with Mitral Stenosis, J. Mt. Sinai Hosp. **8**:754, 1942. (*c*) Hay, W. E., and Levine, S. A.: Age and Auricular Fibrillation as

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They found that rest in bed for a year or more results in a significant decrease in the size of the heart, that bradycardia (1 case) resulted in a slight but definite enlargement and that tachycardia up to rates of 180 to 200 produced no change in size but that rates over 200 may result in considerable cardiac enlargement if long continued. Keith and Brick then studied the changes in the size of the heart during the various stages of a single attack of rheumatic fever in 100 patients. From two to twelve roentgenograms were taken on each patient, and the cardiac surface area on admission was compared with that when progressive change had ceased to occur. They found that in 33 of the patients the heart became larger, in 18 it remained unchanged and in 49 it became smaller. If the patients with pericarditis are left out, the average increase was 8 sq. cm., which was approximately the same as the average decrease, which was 9 sq. cm. The time required for the maximal change to occur was approximately the same (over five months) whether the heart became larger or smaller, indicating that the change is not a sudden process. They found that the heart muscle shows greater recuperative powers than the heart valves and that valvular damage may occur without enlargement of the heart. Criteria are presented which should aid in the differential diagnosis of cardiac dilatation and pericarditis with effusion and carditis and valvulitis.

BACTERIAL ENDOCARDITIS

Streptococcus Viridans Endocarditis.—Hundreds of patients with Str. viridans endocarditis have been treated with one or other of the sulfonamide drugs and sometimes with one of these drugs in combination with heparin, dicoumarin, hyperthermia or typhoid vaccine. Probably all or nearly all of the cures are reported, while many of the failures are not. If consideration is given to the possible error in diagnosis, the rare spontaneous recovery and the possibility of late relapse (some of the cures have not been followed for long), the treatment, though more effective than in the days before the introduction of the sulfonamide compounds, is still disappointing. The high percentage of cures reported by Smith, Sauls and Stone [33] from a review of the literature does not provide an adequate picture. The experience of some investigators suggests that none of the various adjuncts to chemotherapy as yet reported are of proved value or, at least, to be relied on, though further studies are indicated. The single very favorable exception is in patent ductus arteriosus, in which ligation of the ductus forms part of the treatment.[34]

A rational approach to chemotherapy has been presented by Orgain and Poston,[35] who find not only that there are a large number of viridans strains but that there

Independent Factors in Auricular Mural Thrombus Formation, Am. Heart J. **24**:1, 1942. (*d*) Cohn, A. E., and Lingg, C.: The Natural History of Rheumatic Cardiac Disease, Mod. Concepts Cardiovasc. Dis., 1942, vol. 11, no. 7. (*e*) Console, A. D.: The Relation of Cardiac Lesions to Clinical Course of Rheumatic Fever, Arch. Int. Med. **69**:551 (April) 1942. (*f*) Juster, I. R.: The Relationship of Upper Respiratory Infections to Rheumatic Activity in Chronic Rheumatic Heart Disease, Ann. Int. Med. **16**:1137, 1942. (*g*) Burgess, A. M., and Ellis, L. B.: Chest Pain in Patients with Mitral Stenosis, with Particular Reference to So-Called "Hypercyanotic Angina," New England J. Med. **226**:937, 1942.

33. Smith, C.; Sauls, H. C., and Stone, C. F.: Subacute Bacterial Endocarditis Due to Streptococcus Viridans: A Survey of the Present Status of the Previously Reported Cures and a Clinical Study of Fifteen Treated Cases, Including Another Cure, J. A. M. A. **119**:478 (June 6) 1942.

34. Footnotes 24 and 25.

35. Orgain, E. S., and Poston, M. A.: Sulfonamide Compounds in Therapy of Bacterial Endocarditis, Arch. Int. Med. **70**:777 (Nov.) 1942. Poston, M. A., and Orgain, E. S.: A Comparison of the Bacteriostatic Effect of the Sulfonamide Drugs upon the Growth of Twenty-Five Strains of Streptococcus Viridans, Am. J. M. Sc. **203**:577, 1942.

is a great variation in the susceptibility of each strain to the various sulfonamide drugs. They found that sodium sulfapyridine (monohydrate sodium salt of 2-[paraaminobenzenesulfonamido]-pyridine) exhibited the most marked effectiveness against the greatest number of strains and that preliminary in vitro tests are probably of value in determining the drug of choice.

Bacterial Endocarditis Due to Organisms Other Than Str. Viridans.—A number of interesting cases have been reported,[36] in some of which cures were obtained by the use of sulfonamide drugs. Of particular interest are the reports[37] of 2 cases of mycotic endocarditis. Only 6 cases of this condition have thus far been reported in the medical literature, and 5 of the 6 patients were drug addicts (heroin). Contaminated heroin (diacetyl morphine) is considered to be a likely source of infection. Clinically the cases are characterized by rather slow progression with little fever but with development of focal lesions, especially in the brain. Pathologically the vegetations are grafted on scarred or damaged heart valves and are responsible for multiple embolic phenomena. The sulfonamide compounds are of no value.

Goulder and his associates[38] have reported in detail a case of Salmonella suipestifer endocarditis and have briefly reviewed the 3 previously reported cases. The endocarditis was superimposed on previous damage to the heart valves in 3 cases, due to rheumatic infection in 2 and to syphilitic infection in 1. The clinical course was rapidly progressive in each case and characterized by chills and high fever, prostration, bacteremia and leukocytosis (an unusual finding in uncomplicated suipestifer bacteremia). Embolic phenomena and changing heart murmurs occurred in 3 of the 4 cases.

ARTERIAL HYPERTENSION

The large number of studies reported on the mechanism of arterial hypertension in animals and the clinical counterpart in man do not lend themselves to brief review. For a complete account of the present status of the nature of arterial hypertension and its treatment reference should be made to the various review articles which have appeared during the past year.[39] At this time one cannot hope

36. Glazebrook, A. J., and Thomson, S.: Sulfonamide Compounds and Acute Rheumatism, J. Hyg. **42**:20, 1942. Keith, H. M., and Heilman, F. R.: Subacute Bacterial Endocarditis Due to the Hemolytic Streptococcus Lancefield Group G, Proc. Staff Meet., Mayo Clin. **17**:358, 1942. Blumberg, N.; Heine, W. I., and Lipshutz, J.: Pneumococcus (Type XXVIII) Endocarditis with Recovery, J. A. M. A. **120**:607 (Oct. 24) 1942. Orgain, E. S., and Poston, M. A.: Mixed Infections in Bacterial Endocarditis, Am. Heart J. **23**:823, 1942. Hamburger, M., Jr.; Schmidt, L. H.; Ruegsegger, J. M.; Sesler, C. L., and Grupen, E. S.: Sulfonamide Resistance Developing During Treatment of Pneumococcic Endocarditis, J. A. M. A. **119**:409 (May 30) 1942.

37. Pasternack, J. G.: Subacute Monilia Endocarditis, Am. J. Clin. Path. **12**:496, 1942. Wikler, A., and others: Mycotic Endocarditis: Report of a Case, J. A. M. A. **119**:333 (May 23) 1942.

38. Goulder, N. E.; Kingsland, M. F., and Janeway, C. A.: Salmonella Suipestifer Infection in Boston: A Report of Eleven Cases with Autopsy Findings in a Case of Bacterial Endocarditis Due to This Organism, and a Study of the Agglutination Reactions in This Infection, New England J. Med. **226**:127, 1942.

39. (*a*) Goldblatt, H.; Lewis, H. A., and Kahn, J. R.: The Pathogenesis and Treatment of Hypertension: Experimental Observations, in Nelson Loose Leaf Medicine, New York, Thos. Nelson & Sons, 1942. (*b*) Page, I. H.: Studies on the Mechanism of Arterial Hypertension, J. A. M. A. **120**:757 (Nov. 7) 1942. (*c*) Winternitz, M. C.: Some Aspects of the Relation of the Kidneys to Cardiovascular Disease, J. Iowa M. Soc. **32**:157, 1942. (*d*) Lewis, H. A., and Goldblatt, H.: Studies on Experimental Hypertension, Bull. New York Acad. Med. **18**:459, 1942. (*e*) White, B. V.; Durkee, R. E., and Mirabile, C.: Renal Hypertension: A Review of Its Status, Including the Report of a Case of Hypertension Relieved After

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to point out more than some of the recent advances and the present trend in research. In doing this it is important to separate fact from theory and to keep clearly in mind that there may be important differences between the mechanism of the experimental production of hypertension in animals and the mechanism of its occurrence in man.

Experimental Hypertension.—There is no reason to doubt that constriction of the renal arteries in various animals may lead to permanent hypertension due to a humoral mechanism of renal origin. There is good evidence that this hypertension is due to the liberation of a substance, renin, which interacts with another substance, renin activator or hypertension precursor, to form the effective vasoconstrictor agent named angiotonin (Page) or hypertensin (Braun-Mendenez).

Goldblatt and his associates [39a,g] have found that an adequate amount of adrenal cortical tissue is necessary for the liberation or formation of renin activator (hypertensin precursor), as it almost disappears from the systemic blood of untreated adrenalectomized dogs but returns following the administration of desoxycorticosterone acetate. Previous observations by Page on adrenalectomy in experimental hypertension led him to conclude that the adrenal glands were not directly concerned. There is general agreement, however, that the action of renin is not affected by hypophysectomy (recently confirmed by Goldblatt and his co-workers [40]), thyroidectomy, pancreatectomy or gonadectomy.

Much evidence has been adduced in the past to the effect that the vasoconstriction produced by angiotonin is similar to that observed in experimental hypertension. The recent observations of Abell and Page [41] confirm this. By means of moat chambers they were able to observe directly the small vessels in rabbits' ears during the development of experimental renal hypertension. They found that the arterioles became permanently constricted, although not sufficiently to obstruct the blood supply. This constriction occurred whether or not the vessels were supplied with nerves and must therefore have been due to the direct action of some substance. Similar arteriolar responses followed the intravenous injection of angiotonin.

It has also been shown that changes in the intrarenal circulation may be similar in experimental hypertension and after the injection of angiotonin. Since the clearance of diodrast may be decreased while clearance of inulin is well maintained, the characteristic change in intrarenal circulation is thought to consist of a decrease in renal blood flow but an increase in pressure in the glomerular capillaries.

It has further been shown that repeated injections of renin lead to progressive decrease in response because of exhaustion of renin activator (or hypertensin precursor). This phenomenon, called tachyphylaxis, has been thoroughly confirmed.

With regard to the reaction of angiotonin with some further substance there is some difference of opinion. Page has postulated a system of angiotonin

Nephrectomy, New England J. Med. **228**:277, 1942. (*f*) Page, I. H.: Nature of Arterial Hypertension, J. Missouri M. A. **39**:237, 1942. (*g*) Goldblatt, H.; Kahn, J. R., and Lewis, H. A.: Studies on Experimental Hypertension: XVII. Experimental Observations on the Treatment of Hypertension, J. A. M. A. **119**:1192 (Aug. 8) 1942.

40. Goldblatt, H.; Braden, S.; Kahn, J. R., and Hoyt, W. A.: Studies on Experimental Hypertension: XVI. The Effect of Hypophysectomy on Experimental Renal Hypertension, J. Mt. Sinai Hosp. **8**:579, 1942.

41. Abell, R. G., and Page, I. H.: The Reaction of Peripheral Blood Vessels to Angiotonin, Renin, and Other Pressor Agents, J. Exper. Med. **75**:305, 1942; Effects of Renal Hypertension on the Vessels of the Ears of Rabbits, ibid. **75**:673, 1942.

activators and inhibitors, while Braun-Mendenez, Fasciolo and others believe that hypertensin is destroyed by a substance of the nature of an enzyme which is present in normal serum and which they named hypertensinase. That the kidneys are the main source of this inhibitor of angiotonin (or hypertensinase) is shown by the fact that after bilateral nephrectomy the inhibitor tends to disappear from the blood. This is consistent with other evidence that the normal kidney elaborates a substance which reduces blood pressure.

Despite the fact that the normal kidney tends to counteract the hypertensive effect of a contralateral ischemic kidney, the results of treating experimental hypertension by means of renal extracts are uncertain. The technical difficulties in separating fractions which may have a specific physiologic effect are great, and final opinion must await further trial. Wakerlin and his associates [42] have reported some success in the treatment of experimental hypertension by the injection of renin, thereby stimulating the production of "antirenin," but others [43] have failed to confirm their findings.

Another approach has been made to the possible role of the kidneys in hypertension by Bing and Zucker (previously reviewed), who have shown that the ischemic kidney is capable of transforming amino acids, themselves without pressor activity, into the corresponding amines, which have a strong pressor action. In line with this supposition that phenolic amines may be important factors in renal hypertension, Schroeder and Adams [44] found that tyrosinase will destroy angiotonin because tyrosinase is a phenolic oxidase; Schroeder [45] has suggested that angiotonin may contain a phenolic group. It was found that preparations of tyrosinase from mushrooms were effective in lowering the blood pressure not only in animals but in man. That this effect is due to enzymatic activity is questionable in view of the recent observations of Prinzmetal and his associates [46] that heat-inactivated tyrosinase preparations are as effective as active ones in reducing blood pressure in patients with hypertension. It appears likely that the mechanism of the reduction of blood pressure following the administration of the renal extracts and of tyrosinase is no different from that observed following the injection of typhoid vaccine.

Role of the Kidneys in Arterial Hypertension in Man.—There is no doubt that a wide variety of pathologic conditions which have in common a partial reduction of blood flow to one or both kidneys may cause permanent hypertension in man. Such conditions include narrowing of the mouths of renal arteries, aberrant renal arteries, various nephritides, chronic atrophic pyelitis and hydronephrosis. Some

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42. Wakerlin, G. E., and Johnson, C. A.: Reductions in Blood Pressures of Renal Hypertensive Dogs by Hog Renin, Proc. Soc. Exper. Biol. & Med. **46**:104, 1942. Wakerlin, G. E.; Johnson, C. A.; Smith, E. L.; Moss, W. G., and Weir, J. R.: Prophylactic Treatment of Experimental Renal Hypertension with Renin, Am. J. Physiol. **137**:515, 1942. Wakerlin, G. E., and Johnson, C. A.: Antiserum for Renin, Proc. Soc. Exper. Biol. & Med. **44**:277, 1942.

43. Friedman, M.; Kruger, H. E., and Kaplan, A.: Inability of Purified Renin to Reduce the Blood Pressure of Hypertensive Dogs, Proc. Soc. Exper. Biol. & Med. **50**:56, 1942; The Inability of Purified or Crude Kidney Extract (Renin) to Reduce the Blood Pressures of Hypertensive Dogs, Am. J. Physiol. **137**:570, 1942.

44. Schroeder, H. A., and Adams, M. H.: Effect of Tyrosinase upon Experimental Hypertension, J. Exper. Med. **73**:531, 1941.

45. Schroeder, H. A.: Effect of Tyrosinase on Arterial Hypertension, Science **93**:116, 1941.

46. Prinzmetal, M.; Alles, G. A.; Margoles, C.; Kayland, S., and Davis, D. S.: Effects on Arterial Hypertension of Heat-Inactivated Tyrosinase Preparations, Proc. Soc. Exper. Biol. & Med. **50**:288, 1942.

recent references to such conditions are listed below.[47] These conditions probably represent the clinical counterpart of experimental renal hypertension.

With respect to essential hypertension, the causal relation to the kidneys is not wholly clear but a concept of the mechanism and of the part the kidneys play has been summarized by Schroeder.[48] He begins by pointing out the well known fact that individual susceptibility is an important factor in the development of essential hypertension and that this susceptibility is usually declared by an excessive vascular response to emotional stimuli. This "defect" may be hereditary or the result of early environmental influences. He then points out that the injection of epinephrine hydrochloride results in prolonged renal vasoconstriction and that psychic stimulation (anxiety) can apparently do the same. The possibility therefore exists that often repeated or prolonged psychic stimulation in predisposed persons may cause a sufficient degree of renal ischemia to result in hypertension. Such hypertension would be temporary at first but after a time might lead to permanent hypertension as a result of damaging the renal arterioles. Schroeder believes that the foregoing concept may account for the variations in the clinical course so frequently observed.

Treatment of Essential Hypertension in Man.—There is little which is new to report with respect to the treatment of essential hypertension. Potassium sulfocyanate continues to enjoy considerable favor despite occasional untoward effects, and it is said to be particularly effective following splanchnicectomy. Further experience with extracts of kidney tissue have yielded disappointing results, and the general opinion is that these extracts are no more effective than are certain other organ extracts. Tyrosinase apparently causes lowering of the blood pressure but not by its enzymatic action; further trial is warranted. The most consistently good results have been obtained following splanchnicectomy with use of the newer technics. In properly selected cases the results are indeed gratifying, and work carried out by Smithwick in Boston, as yet unpublished, has already achieved important results.

CORONARY HEART DISEASE

Precipitating Factors of Myocardial Infarction.—All cardiologists agree that myocardial infarction may be precipitated by certain specific events, but there is wide disagreement with regard to the nature of some of these events and the frequency of their occurrence. This question is of great and immediate clinical importance for at least two reasons: (1) the desire properly to advise patients known to have or suspected of having coronary heart disease how best to avoid cardiac infarction and (2) the medicolegal aspects concerned in the relation of

47. Simonds, J. P.: Renal Pathologic Changes in Hypertension and Glomerulonephritis, J. A. M. A. **120**:89 (Sept. 12) 1942. Braasch, W. F.: Surgical Kidney as Etiologic Factor in Hypertension, Canad. M. A. J. **46**:9, 1942. Fishberg, A. M.: Hypertension Due to Renal Embolism, J. A. M. A. **119**:551 (June 13) 1942. Farrell, J. I., and Young, R. H.: Hypertension Caused by Unilateral Renal Compression, ibid. **118**:711 (Feb. 28) 1942. Hoffman, B. J.: Renal Ischemia Produced by Aneurysm of Abdominal Aorta, ibid. **120**:1028 (Nov. 28) 1942. Wilson, C. L., and Chamberlain, C. T.: Unilateral Renal Ischemia Associated with Hypertension, J. Urol. **47**:421, 1942. Baerøe, K.: Hypertension as Result of Renal Ischemia in Dissecting Aneurysm of Aorta, Nord. med. (Norsk mag. f. lægevidensk.) **12**:3408, 1941. Prinzmetal, M.; Hiatt, N., and Tragerman, L. J.: Hypertension in a Patient with Bilateral Renal Infarction: Clinical Confirmation of Experiments in Animals, J. A. M. A. **118**:44 (Jan. 3) 1942. Friedman, B.; Moschkowitz, L., and Marrus, J.: Unilateral Renal Disease and Renal Vascular Changes in Relation to Hypertension in Man, J. Urol. **48**:5, 1942. Everett, H. S., and Scott, R. B.: Possible Etiologic Role of Gynecologic Lesions in Production of Hypertension, Am. J. Obst. & Gynec. **44**:1010, 1942.

48. Schroeder, H. A.: "Essential" Hypertension: A Concept of Its Mechanism, Am. J. M. Sc. **204**:734, 1942.

accidents to cardiac infarction. To answer the question it is necessary to learn as much as possible of the natural history of this important cardiac complication. Attempts at analyzing the large amounts of clinical data which bear on the problem and to correlate the results of the various authors have proved difficult because of (1) the differences in the nomenclature used, (2) the failure on the part of some to establish the diagnosis of myocardial infarction in the cases reported, (3) the lack of specific criteria or the use of obviously false criteria in attempting to show a causal connection between myocardial infarction and various antecedent events and (4) the desire to bolster this or that theory rather than to seek the truth.

During the past few years much has been written on this subject and a number of articles reviewed. Some recent reports [49] are also of interest. At the present time it seems fair to conclude that myocardial infarction due to coronary thrombosis or to prolonged ischemia in the presence of coronary narrowing without thrombosis may be precipitated by (1) sudden severe effort or prolonged effort of less severity, (2) emotion, particularly if severe or prolonged, (3) various factors which lead to a fall in blood pressure and (4) blows on the chest.

Clinical Features of Coronary Occlusion and of Myocardial Infarction.—It is well recognized that in a relatively large number of the patients the onset of frank myocardial infarction is preceded by certain premonitory symptoms. These symptoms may be due to the sudden occlusion or narrowing of a coronary vessel without infarction, or if infarction is found, it is small and does not produce the classic symptom complex. Boyer [50] emphasizes the importance of recognizing these prodromal symptoms and the need for instituting immediate and adequate treatment. He illustrates his report with the details of 7 cases which fall into three patterns so far as the symptom of pain is concerned. The first is that of a patient who has pain sufficiently characteristic of coronary occlusion or myocardial infarction but in whom the syndrome of infarction does not at first appear; as a result, some diagnosis other than coronary insufficiency may be made. The second pattern is that of the sudden onset of angina pectoris in a patient previously well, and the third, the sudden increase in severity and frequency of anginal symptoms. In all of these instances the probability of imminent infarction should be considered. Concerning the coronary circulation and the time necessary for the development of collateral circulation, Boyer concludes that two to three weeks of rest in bed, sedation, adherence to a light diet, avoidance of tobacco and possibly papaverine should be prescribed. Not every one will agree with respect to rest in bed; it is the definite impression of some that a little activity is preferable, but the final answer has not been given.

Shillito, Chamberlain and Levy [51] have made a careful study of the cardinal diagnostic features of myocardial infarction in 50 uncomplicated cases seen very early in the attack. A friction rub was heard in 20 per cent, gallop rhythm in 28

49. Boas, E. P.: Some Immediate Causes of Cardiac Infarction, Am. Heart J. **23**:1, 1942. Leinoff, H. D.: Acute Coronary Thrombosis in Industry: II. Indirect Injuries from Toxic Gases and Other Physical Agents, ibid. **24**:187, 1942. Jokl, E., and Suzman, M. M.: Mechanisms Involved in Acute Fatal Nontraumatic Collapse Associated with Physical Exertion, ibid. **23**:761, 1942. Sigler, L. H.: Trauma of the Heart Due to Nonpenetrating Chest Injuries, J. A. M. A. **119**:855 (July 11) 1942. Leinoff, H. D.: Acute Coronary Thrombosis in Industry, Arch. Int. Med. **70**:33 (July) 1942. Willius, F. A.: Cardiac Clinics: Certain Medicolegal Aspects of Coronary Thrombosis, Proc. Staff Meet., Mayo Clin. **17**:521, 1942.

50. Boyer, N. H.: Premonitory Symptoms of Myocardial Infarction, New England J. Med. **227**:628, 1942.

51. Shillito, F. H.; Chamberlain, F. L., and Levy, R. L.: Cardiac Infarction: The Incidence and Correlation of Various Signs, with Remarks on Prognosis, J. A. M. A. **118**:779 (March 7) 1942.

per cent, a fall in systolic blood pressure (20 mm. or more) in 74 per cent, an elevation of venous pressure in 76 per cent, significant electrocardiographic alterations in 86 per cent, leukocytosis in 96 per cent, tachycardia (rate over 80) in 98 per cent, increased sedimentation rate in 98 per cent and fever in every instance. With respect to the last four signs, elevation of the sedimentation rate was the last to occur (third day) but persisted the longest. A rectal temperature above 104 F., a white blood cell count higher than 25,000 or a venous pressure over 200 mm. of water indicated a grave prognosis; 7 of 8 patients showing one or another of these signs died within sixteen days after the onset of the attack.

With regard to the immediate mortality in cases of acute myocardial infarction, Levine [52] rightly points out that the figures usually given are from series of cases seen in general hospitals and by consultants, which are apt to be more serious than those commonly seen in general practice. The immediate mortality (death within several weeks) was 33 per cent in Levine's series and 47 per cent in that of Woods and Barnes [53]; Levine believes that the mortality might well prove to be 20 per cent or less if a truly representative series of cases were analyzed. Both Levine and Woods and Barnes agree that age is the most important factor influencing the immediate mortality and that there is little or no difference whether the infarction is in the anterior or in the posterior wall of the heart. Sex is not a very important factor if age is taken into account. The prognosis was found to be better if the electrocardiographic changes were slight (Levine) and much worse in cases in which the position of the infarct could not be localized (Woods and Barnes). The latter workers believe that ventricular extrasystoles are likely to be followed by ventricular tachycardia and not infrequently by ventricular fibrillation, but Levine did not find "simple extrasystoles" to be very important. All agree, however, that the more serious arrhythmias affect the prognosis unfavorably. Other unfavorable factors which Levine mentions are hypertension, fall of blood pressure, especially to levels below 80 mm., pericarditis and congestive failure. He found, as did Shillito and his co-workers,[51] that a high fever, a rapid heart rate and a high white blood cell count are likewise unfavorable factors.

With respect to the ultimate prognosis, Levine [52] found that the average survival period of patients who recovered from their initial attack of myocardial infarction was forty-one and one-tenth months for 101 patients who were known to be dead and twenty-seven and six-tenths months for 271 patients who were found to be still living. The age of the patient was one of the most important factors; the younger patients lived longer. Sex was also very important; the average survival time for women was only eighteen and three-tenths months, compared with forty-three and one-tenth months for men. There was no difference with respect to those who had infarctions of the anterior wall and those who had infarctions of the posterior wall. Of the 80 patients whose mode of death was known, 40 per cent died of a subsequent attack of coronary thrombosis, 35 per cent died instantly, 20 per cent died of congestive failure and only 5 per cent succumbed to causes unrelated to the heart. Levine found that in no less than 75 per cent of 354 cases a return to partial or full duty for an appreciable time was possible.

Infarction of the Auricles of the Heart.—Cushing and his associates [54] have reported their clinical and experimental observations on auricular infarction.

52. Levine, S. A.: The Prognosis of Coronary Occlusion. Part I and Part II: Ultimate Prognosis, Mod. Concepts Cardiovasc. Dis., 1942, vol. 11, nos. 5 and 6.

53. Woods, R. M., and Barnes, A. R.: Factors Influencing Immediate Mortality After Acute Coronary Occlusion, Am. Heart J. **24**:4, 1942.

54. Cushing, E. H.; Feil, H. S.; Stanton, E. J., and Wartman, W. B.: Infarction of the Cardiac Auricles (Atria), Brit. Heart J. **4**:17, 1942.

During a seven year period of investigation, when the auricles at necropsy were specifically examined for infarcts they were found to be involved in 31 (17 per cent) of 182 cases of myocardial infarction. It is remarkable that the infarction involved the right auricle in 27 cases and the left in only 5. Most of the infarcts occurred in the auricular appendages. Gross occlusion of the auricular arteries was observed in only 1 case. However, partial or complete occlusion of a main coronary vessel was noted in 23 of the 31 cases, and a fresh or a healed ventricular infarct was present in 22 cases, in all of which it was in the left ventricle or the interventricular septum. Acute diffuse myocarditis was present in 2 cases and chronic myocarditis in 1; in the remaining 6 auricular infarcts were the only lesions other than hypertrophy. The gross appearance of the auricular infarcts was similar to that commonly seen in the ventricles, and in 26 cases mural thrombi were adherent to the endocardium over the infarcted area.

Electrocardiograms were taken in 23 cases of auricular infarction, and in 74 per cent of these the auricular mechanism was abnormal, whereas the auricular rhythm was disturbed in only 8 per cent of 91 cases of ventricular infarction without associated infarction of the auricles. The electrocardiographic abnormalities in the patients with auricular infarcts were auricular fibrillation (9 cases), auricular premature beats (4 cases), auricular flutter (2 cases), sinus arrest (1 case) and wandering pacemaker (1 case). Depression of the PQ level occurred in 5 instances, but the authors consider it of doubtful significance because of its occurrence in normal persons. They concluded that an abnormality in the auricular mechanism is the most reliable clue to the clinical diagnosis of infarction of the atriums.

Angina Pectoris.—Reference is made below to a number of articles [55] dealing with various clinical aspects of angina pectoris. Of particular interest are the reports [56] concerned with the diagnostic value of certain electrocardiographic changes after exercise.

The diagnosis of angina pectoris rests on the subjective phenomenon pain. This pain is not always typical, and the differential diagnosis between pain of cardiac and pain of noncardiac origin may be difficult or even impossible. Approximately one quarter of the patients with angina pectoris show no physical abnormality of the heart by any of the usual methods of examination. Because of this any objective evidence of coronary insufficiency is helpful in diagnosis; it indicates that at least the pain *could* be of cardiac origin. Many investigators over the past few years have shown that significant electrocardiographic alterations

55. Wolferth, C. C., and Edeiken, J.: The Differential Diagnosis of Angina Pectoris with Special Reference to Esophageal Spasm and Coronary Occlusion, Pennsylvania M. J. **45**:579, 1942. Barnes, A. R., and Pruitt, R. D.: Problems in the Differential Diagnosis of Coronary Sclerosis, J. Michigan M. Soc. **41**:943, 1942. Heaton, T. G.: Conception of Neuralgic Chest Pain, Canad. M. A. J. **47**:535, 1942. Elek, S. R., and Katz, L. N.: Some Clinical Uses of Papaverine in Heart Disease, J. A. M. A. **120**:434 (Oct. 10) 1942. Perlow, S.: Paravertebral Alcohol Injection for Relief of Cardiac Pain, Illinois M. J. **81**:35, 1942. Jones, C. M., and Chapman, W. P.: Studies on the Mechanism of the Pain of Angina Pectoris with Particular Relation to Hiatus Hernia, Tr. A. Am. Physicians **57**:139, 1942. Lesser, M. A.: The Treatment of Angina Pectoris with Testosterone Propionate: Further Observations, New England J. Med. **228**:185, 1942. Neuwahl, F. J.: Nicotinic Acid in the Treatment of Angina Pectoris, Lancet **2**:419, 1942.

56. Scherf, D.: Exercise Test in Coronary Stenosis, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **5**:2, 1942. Patterson, J. E.; Clark, T. W., and Levy, R. L.: A Comparison of Electrocardiographic Changes Observed During the "Anoxemia Test" on Normal Persons and on Patients with Coronary Sclerosis, Am. Heart J. **23**:837, 1942. Master, A. M.; Dack, S., and Jaffe, H. L.: Cardiac Efficiency and Prognosis Following Recovery from Acute Coronary Occlusion: The Results of Various Functional Tests, J. A. M. A. **120**:1271 (Dec. 19) 1942.

may be recorded during spontaneous or induced attacks of anginal pain in patients with heart disease. The commonest method of inducing attacks is to ask the patient to exercise and thereby put a greater load of work on the heart. Induced anoxemia has also been used. Neither method found great favor, partly because of the lack of definite criteria in evaluating the results. This objection is being overcome. Recently, Twiss and Sokolow [57] were able to obtain significant electrocardiographic alterations after exercise in 56 per cent of patients with angina pectoris irrespective of the presence or the absence of pain. They found that the significant changes are:

> . . . S-T segment depression or elevation of 1.0 mm. or more in Lead I, of 1.5 mm. or more in Lead II, of 1.5 mm. or more in Lead III, and 2.0 mm. or more in Lead IV; or the conversion of an upright to a diphasic or inverted T wave in Lead I, II, or IV; or the development of bundle branch block. If any one of these changes occurs, the electrocardiogram is considered abnormal.

CONGESTIVE HEART FAILURE

A number of interesting articles have appeared dealing with the mechanism of heart failure [58] and the recent developments in treatment.[59]

Boyer and White [59a] have reported 4 instances in which pain in the right upper quadrant of the abdomen, precipitated by exertion and relieved by rest, has been the presenting symptom of early right-sided heart failure. It is evidently due to acute congestion of the liver and is comparable to dyspnea on effort in early left-sided heart failure. Direct questioning of a group of 40 patients who already had clinically evident right-sided failure or were likely candidates for it revealed that the pain had been present at some time in about 45 per cent. It is a symptom to which the patient rarely attaches much significance, since it is usually of little severity and is overshadowed by more uncomfortable symptoms; it is an important though little recognized clue.

Digitalis Preparations.—Eggleston and Gold [60] have clearly described the extensive changes in the twelfth revision of the United States Pharmacopeia with respect to digitalis.

The greatest uniformity in the strength of digitalis preparations is assured by assaying these preparations against a standard material, the Digitalis Reference

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57. Twiss, A., and Sokolow, M.: Angina Pectoris: Significant Electrocardiographic Changes Following Exercise, Am. Heart J. **23**:498, 1942.

58. Katz, L. N.: Mechanism of Heart Failure, J. Mt. Sinai Hosp. **8**:668, 1942. Seymour, W. B.; Pritchard, W. H.; Longley, L. P., and Hayman, J. M., Jr.: Cardiac Output, Blood and Interstitial Fluid Volumes: Total Circulating Serum Protein, and Kidney Function During Cardiac Failure and After Improvement, J. Clin. Investigation **21**:229, 1940. Proger, S.; Ginsburg, E., and Magendantz, H.: The Effects of the Ingestion of Excessive Amounts of Sodium Chloride and Water on Patients with Heart Disease, Am. Heart J. **23**:555, 1942. Stewart, H. J.: Mechanism of Diuresis: Alterations in the Specific Gravity of the Blood Plasma with Onset of Diuresis in Heart Failure, J. Clin. Investigation **20**:1, 1941. Krauel, G.: Influence of Nutrition on Circulating Quantity of Blood: Deficient and High Sodium Chloride Content of Diet, Ztschr. f. klin. Med. **139**:459, 1941. Altschule, M. D., and Zamcheck, N.: Studies of the Circulation and Respiration in a Patient with Anasarca Following Administration of Cortin and Sodium Chloride, J. Clin. Endocrinol. **11**:269, 1942.

59. Gold, H.: Some Recent Developments in Drug Therapy, North End Clin. Quart. **2**:5, 1941. DeGraff, A. C.: Evaluation of Drugs Used in the Treatment of Cardiovascular Diseases, Bull. New York Acad. Med. **18**:246, 1942. Freedberg, A. S., and Blumgart, H. L.: Medical Progress: Digitalis, Edema and Diuretics, New England J. Med. **227**:874, 1942. Gold, H.: Recent Developments in Digitalis, Mod. Concepts Cardiovasc. Dis., 1942, vol. 12, no. 4.

59a. Boyer, N. H., and White, P. D.: Right-Upper-Quadrant Pain on Effort: An Early Symptom of Failure of the Right Ventricle, New England J. Med. **226**:217, 1942.

60. Eggleston, C., and Gold, H.: What the U. S. Pharmacopoeia XII Means to the Physician, Am. J. M. Sc. **203**:759, 1942.

Standard of the Pharmacopeia, and 0.1 Gm. (1½ grains) of this digitalis powder is defined by the Pharmacopeia as 1 U. S. P. unit. The standard powder is supplied by the Pharmacopeia to those who standardize digitalis. The physician may then expect that if he administers 1 U. S. P. unit of digitalis powder or of a tincture of digitalis or of some water-soluble injectable solution, the effects of each in man will be identical, since each will represent the effect of one and the same thing, namely 0.1 Gm. (1½ grains) of the Digitalis Reference Standard. The amount by weight or measure matters little. In one case it might be 2 cc. of a solution and in another case 1 cc. What does matter is that the same amount of potent material is administered, and this can be insured by determining dosage in terms of U. S. P. units. For those who have been thinking in terms of cat units, it might be stated that 0.1 Gm. (1½ grains) of the U. S. P. Digitalis Reference Standard or 1 U. S. P. unit will represent approximately 1.3 cat units. In the case of the solutions of ouabain and strophanthin for parenteral administration the dose of the drug is expressed in milligrams, without reference to any unit, and both are assayed against the Ouabain Reference Standard of the Pharmacopeia, a pure crystalline material.

Sokolow and his associates [61] have reported their studies on the use of digitalis in the prevention of cardiac failure in patients with sinus rhythm. Four ambulatory patients with sinus rhythm, who had previously shown congestive heart failure, were studied for periods varying from thirty-one to sixty weeks. Each was kept on a comparable controlled regimen of activity, salt, fluid and caloric intake. The only variable was the administration or the omission of digitalis. In every instance cardiac failure recurred when digitalis was withheld. They concluded, therefore, that the administration of digitalis tends to prevent the development of failure in patients with sinus rhythm. Digitalis was also of value in relieving the congestive failure produced in these ambulatory patients by withdrawal of the drug.

Flaxman [62] has made a clinical study of the value of digitalis therapy in patients with heart failure due to hypertension or to coronary arteriosclerosis. He found that digitalis is of great value in treatment even when the rhythm is normal. With both types of patients, digitalis was most effective in those showing isolated failure of the left ventricle and a normal heart rate.

A number of articles [63] have appeared on the use of one or another of the purified glucosides of digitalis. These preparations have been shown to be just as effective as the preparations of digitalis now in common use. Digoxin (a purified

61. Sokolow, M.; Weinberg, H. B.; Plaut, J. L., and Katz, L. N.: Digitalis in the Prevention of Recurrent Cardiac Failure in Patients with Sinus Rhythm, Ann. Int. Med. **16**:427, 1942.

62. Flaxman, N.: Clinical Value of Digitalis in Hypertensive Heart Failure: I. With a Normal Rate and a Regular Rhythm, Am. J. M. Sc. **203**:741, 1942; II. With Sinus Tachycardia, ibid. **203**:747, 1942; Digitalis in Arteriosclerotic (Coronary) Heart Failure, J. A. M. A. **119**:252 (May 16) 1942.

63. Rose, O. A.; Batterman, R. C., and DeGraff, A. C.: Clinical Studies on Digoxin, a Purified Digitalis Glycoside, Am. Heart J. **24**:435, 1942. Gold, H.; Kwit, N. T.; Cattell, McK., and Travell, J.: Studies on Purified Digitalis Glycosides: IV. The Single Dose Method of Digitalization, J. A. M. A. **119**:928 (July 18) 1942. Batterman, R. C.; Holman, D. V., and DeGraff, A. C.: The Therapeutic Effectiveness and Potency of Digilanid in the Treatment of Congestive Heart Failure, Ann. Int. Med. **14**:2058, 1941. Batterman, R. C.; Rose, O. A., and DeGraff, A. C.: The Combined Use of Ouabain and Digitalis in the Treatment of Congestive Heart Failure, Am. Heart J. **20**:443, 1940. Sokolow, M., and Chamberlain, F. L.: Cedilanid with Special Reference to Its Intravenous Use, ibid. **23**:243, 1942. Chamberlain, F. L., and Sokolow, M.: Clinical Experience with the Oral Administration of Cedilanid, and a Comparison of the Oral and Intravenous Preparations of Cedilanid with Digitalis Purpurea, ibid. **23**:245, 1942. Tandowsky, R. M.: Electrocardiographic and Clinical Study of Lanatoside C., ibid. **24**:472, 1942.

glucoside of Digitalis lanata) has the advantages of constant potency and quick action but cannot be used conveniently in ambulatory cases. Lanatoside C, or cedilanid (a crystalline glucoside of Digitalis lanata) has the advantages of constant potency and quick action but requires more careful attention with respect to regularity of dosage than do preparations of Digitalis purpurea leaf (digitalis U. S. P.) and may therefore not be as satisfactory for ambulatory patients.

Mercurial Diuretics.—The action and the toxicity of the mercurial diuretics have been thoroughly discussed in several articles.[64]

An immediate acute reaction characterized by dyspnea and the symptoms of shock has led to death in 26 reported cases. In most of the instances the exact cause of death was thought to be cardiac failure, probably the result of ventricular fibrillation. In each case death occurred following the intravenous administration of the drug. Other types of reaction may result from the toxicity of digitalis owing to the mobilization of this drug in patients previously digitalized and to disturbances of salt and water metabolism. Although all of these possibilities must be kept in mind when one is using the drug, it should be emphasized that toxic reactions are extraordinarily rare and should not limit use of this drug.

MISCELLANEOUS

Isolated Myocarditis.—Occasionally heart failure with fatal termination is observed in a young person for which no cause can be found either during life or at necropsy. Saphir [65] has made an interesting study of 15 such cases which were discovered in the routine examination of 5,626 hearts at autopsy. Clinically, the picture was that of cardiac enlargement and progressive heart failure without obvious cause. Pathologically, Saphir found 1 instance of isolated myocarditis of the granulomatous variety and 14 instances of diffuse myocarditis. The heart with granulomatous myocarditis was not definitely enlarged, and throughout the myocardium there were irregular yellowish white areas. Microscopically, giant cells were observed together with a diffuse infiltration of eosinophils and lymphocytes in the myocardium. Neither spirochetes nor tubercle bacilli could be demonstrated. In 12 of the 14 remaining cases in which clinical data could be obtained, the heart was enlarged and dilated. The myocardium was pale gray, with minute grayish streaks or larger areas of gray and white. Microscopically, the lesions were diffuse, with lymphocytes and endothelial leukocytes predominating. These lesions did not resemble those of any clearly defined type of myocarditis.

Interstitial Myocarditis Due to Sulfonamide Compounds.—French and Weller [66] discovered a significant degree of interstitial myocarditis in 126 of 283 patients who had received one of the sulfonamide compounds (5 to 200 Gm.) during the last few weeks of life. Interstitial myocarditis was not present in any patient who had not received chemotherapy for at least thirty days prior to death. The changes observed were not macroscopic but microscopic and were characterized by paravascular cellular infiltrations of eosinophils and other cells. Eosinophilic

64. DeGraff, A. C., and Lehman, R. A.: The Acute Toxicity of Mercurial Diuretics, J. A. M. A. **119**:998 (July 25) 1942. Kline, E. M., and Seymour, W. B.: Systemic Reactions to Mercurial Diuretics, Am. J. M. Sc. **203**:874, 1942. DeGraff, A. C.; Batterman, R. C., and Lehman, R. A.: Limiting Content of Theophylline Necessary to Prevent Local Toxic Action of Mercurial Diuretics, Proc. Soc. Exper. Biol. & Med. **38**:373, 1938. DeGraff, A. C.; Batterman, R. C., and Lehman, R. A.: The Influence of Theophylline upon the Absorption of Mercupurin and Salyrgan from the Site of Intramuscular Injection, J. Pharmacol. & Exper. Therap. **62**:26, 1938.

65. Saphir, O.: Isolated Myocarditis, Am. Heart J. **24**:167, 1942.

66. French, A. J., and Weller, C. V.: Interstitial Myocarditis Following Clinical and Experimental Use of Sulfonamide Drugs, Am. J. Path. **18**:109, 1942.

infiltrations were also sometimes observed in the liver, the lungs and the kidneys. Similar eosinophilic interstitial myocarditis was observed in mice and rats receiving daily intraperitoneal injections of sulfonamide drugs. French and Weller point out that the lesions are reversible and that the eosinophilic character make drug idiosyncrasy a likely cause. They emphasize the importance of frequent and careful evaluation of the cardiovascular status of patients receiving sulfonamide drugs.

Tumors of the Heart.—Beck [67] has published 2 case reports of unusual interest in which he describes the removal of tumors from in and around the heart. The first case was that of a young man 22 years of age who for two years periodically complained of fever, dyspnea, weakness and pain in the chest and had been temporarily relieved after repeated aspiration of fluid, presumably from the pericardium. Because of the persistence of a cystlike structure on the right side of the heart, operation was performed and a cyst containing 300 cc. of coagulated material found. It was emptied and washed and the margin of the cyst sutured to the pectoral muscle. The patient improved, but in two years the symptoms recurred, and at a second operation a cystic teratoma was found attached to the wall of the heart and great vessels. Beck states, "I had the impression that the wall of the cyst was fused with the parietal pericardium." However, it was not clearly certain from Beck's report that the cyst was intrapericardial. Beck briefly describes 4 other cases previously reported.

Beck's second case was that of a man 39 years of age who complained of progressively increasing dyspnea and pain in the chest on exercise over a period of six years. The clinical studies of Drs. Feil and Friedman led to the diagnosis of cardiac tumor. Beck thought that the tumor was probably benign. At operation a large, subepicardial tumor was removed. It consisted of a capsule of calcified connective tissue filled with cheesy material. The patient was well eighteen months after the operation and apparently cured. Beck remarks that this was the first time that a benign tumor of the heart was recognized clinically and the only time that removal was carried out.

Thiamine Chloride Deficiency and the Circulation.—That cardiac enlargement and failure may result from deficiency of vitamin B_1 is well known, and studies along this line are being reported continually.[68] Less well known are the cardiovascular changes resulting from slight or early stages of thiamine deficiency and the time required for their appearance. Johnson and his associates [69] have shown that in healthy persons performing manual labor the signs of vitamin B_1 deficiency may appear in a few days. The reason for the earlier appearance of symptoms in persons doing hard work is that the increased carbohydrate metabolism uses up larger amounts of thiamine. The evidence for decreased cardiovascular efficiency is seen in the reduced performance in tests the limiting factor of which is the cardiovascular system.

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67. Beck, C. S.: An Intrapericardial Teratoma and a Tumor of the Heart: Both Removed Operatively, Ann. Surg. **116**:161, 1942.

68. Hussey, H. H., and Katz, S.: Beriberi Heart Disease and Pulmonary Embolism: Report of Three Cases, M. Ann. District of Columbia **11**:247, 1942. Rascoff, H.: Beriberi Heart in a Four Month Old Infant (with Four Year Follow-Up), J. A. M. A. **120**:1292 (Dec. 19) 1942. Garland, L. H., and McKenney, A. C.: Roentgen Diagnosis of Vitamin Deficiency Cardiac Conditions, with Some Clinical Observations on Thiamin Deficiency, Radiology **38**:426, 1942. Moniz de Bettencourt, J.: Circulatory Disorders Due to Avitaminosis B_1: Review of Literature, Amatus **1**:247, 1942.

69. Johnson, R. E.; Darling, R. C.; Forbes, W. H.; Brouha, L.; Egana, E., and Graybiel, A.: Effects of Diet Deficient in Part of Vitamin B Complex on Men Doing Manual Labor, J. Nutrition **24**:585, 1942.

Heart in Sickle Cell Anemia.—It is thought by some that the cardiac changes in sickle cell anemia are specific, but Klinefelter,[70] on the basis of a careful study of 12 cases, concludes that no cause other than the profound anemia is responsible. Of particular interest are the similarities between the clinical findings in certain cases of sickle cell anemia and those in cases of rheumatic fever. Both may show exacerbations following infection of the respiratory tract, pain and swelling in the joints (which is often migratory), fever and leukocytosis, tachycardia, cardiac enlargement, prolongation of the PR interval in the electrocardiogram, and systolic and diastolic murmurs. They differ among other things in that the pain in sickle cell anemia is often along the bones, that it is not relieved by salicylates and that ulcers of the leg are common in sickle cell anemia.

Chronic Constrictive Pericarditis.—Harrison and White[71] have analyzed 37 cases of chronic constrictive pericarditis seen by themselves. The later results in 15 of the cases which were reported in 1935 are given, together with a brief clinical survey of the course of illness in 22 additional cases. The ages of the patients ranged from 10 to 59 years. The average age of those operated on was 28.8 years, and the average age of those not operated on was 45.5 years. There were 25 males and 12 females. Tuberculosis was apparently the cause in 5 cases, sepsis in 1, pneumonia with polyserositis in 2; in the other 29 cases the cause was unknown or questionable. In 19, or 54 per cent, of the cases, the cardiac area was enlarged roentgenologically; in 18 the size of the heart was normal. In 9 of the total number of cases there was an apical systolic murmur. In 16, or 43 per cent, there was calcification of the pericardium. The electrocardiogram was abnormal in all cases. The chief abnormalities were: low voltage of the QRS waves in all three classical leads in 22, or 60 per cent, of the 37 cases; abnormal T waves of two or three of the classical leads in all cases; auricular fibrillation in 14, or 37 per cent, of the series, and auricular flutter in 1 case. The axis deviation was normal in almost all instances.

Twenty-eight of the 37 patients were treated by pericardial resection. Fourteen of the 28 were clinically cured, although in a few there remained a slight increase in venous pressure above the average normal and 1 of the 14 died of another cause one year after operation. Three other patients were much improved by the operation. Two died primarily of the disease itself, 1 of tuberculosis soon after the operation and 1 in congestion four months after operation. In 5 patients the death was related to the operation; two of the 5 succumbed on the day of operation, 1 died one day after operation, 1 died of pulmonary embolism two days after operation, and 1 died of bronchopneumonia six days after operation. Four died of other complications. Nine patients did not have pericardial resection: In 3 of these the disease was so mild that operation was not thought necessary, 3 were too sick to undergo operation, 1 died of miliary tuberculosis before the operation could be carried out, 1 died before this series of operations was started, and 1 was lost sight of.

70. Klinefelter, H. F.: The Heart in Sickle Cell Anemia, Am. J. M. Sc. **203**:34, 1942.

71. Harrison, M. B., and White, P. D.: Chronic Constrictive Pericarditis: A Follow-Up Study of Thirty-Seven Cases, Ann. Int. Med. **17**:790, 1942.

Book Reviews

Mental Health in College. By Clement C. Fry, M.D., with the collaboration of Edna C. Rostow. Pp. 365. Price, $2. New York: The Commonwealth Fund, 1942.

This work represents a survey of the case histories of some 1,257 university students who came under the observation of the authors in over a decade of experience at Yale University. The first third of the book is concerned with a definition of the problem, a description of the materials of the study and a general discussion of "the problems of personality growth." The student environment at Yale University is then described (perhaps the most interesting part of the book), followed by a consideration of the psychiatric problems encountered by students of the various schools and departments in their personal, scholastic and social adjustments.

The book is informative and interesting as a general survey of the types of maladjustment seen among the students at an old, aristocratic university, where social factors are at least as important as the academic. It reveals much about Yale University as well as about the students. As a sociologic study the book has considerable value. As a contribution to psychiatric thought it is barren. Superficiality marks the discussion of individual case histories, none of which seems to have been extended to the point where the psychiatrist really understood his patient's inner psychologic problems. Perhaps little more was possible in view of the limited time available under the circumstances. Though the discussion of the importance of family relationships in the mental life of the student is good, the consideration of the sexual growth and behavior of the student only skims the surface. The important subject of treatment of patients with sexual problems is often dismissed with little more than such meaningless and vague statements as that "Treatment . . . was directed at giving him a more informed attitude toward sex and increasing his insight into his whole personality." Sexual maladjustments are frequently attributed to "inadequate sexual information," and "a thorough education about sex" is often considered the correct treatment. Such statements may cover adequate management of these delicate problems, but they certainly do not tell the reader anything specific.

In general, the book is an interesting survey of the field, but it is of little value in helping to solve the problems it reveals.

Sulfanilamide and Related Compounds in General Practice. Second edition. By Wesley W. Spink, M.D., F.A.C.P. Price, $3.00. Pp. 374. Chicago: The Year Book Publishers, Inc., 1942.

That the second edition of this book came out only a comparatively few months after the first edition speaks well for its authenticity as well as for its completeness. Very rapidly Spink's book on the sulfonamide compounds obtained popularity, and fortunately so, because this has enabled him to bring out a new edition in which he has been able to incorporate the rapidly evolving newer developments in therapy with these compounds that have taken place since the appearance of the first edition.

The second edition has undergone a complete revision; not only has new material been added, but some of the older material has been elaborated on and some has been deleted. This is, of course, in line with the advances that have taken place in therapy with sulfonamide drugs and the development of newer compounds by the chemists who have been working with these drugs.

The book has much to recommend it. It is reasonably short and concise but nevertheless sufficiently detailed to allow the practitioner to obtain all the information he may need for the treatment of certain diseases against which sulfonamide compounds have proved effective. For the investigator the very complete bibliography is sufficient to refer him to source material and to a more complete exposition than can be given in a relatively small book.

With practically all the details of treatment the reviewer is in accord. He is not in agreement, however, with a part of the chapter which has to do with prophylactic use of the sulfonamide compounds. He wishes that Spink had condemned rather than accepted the rather promiscuous use of these potent and sometimes dangerous drugs in the prevention of hypothetic complications of various conditions, which will probably never develop and which if they do can be minimized by one or another of the sulfonamide preparations.

Oleoperitoneografia: Contribución al estudio radiológico del peritoneo. By Carlos H. Niseggi, Profesor Adjunto de Radiología de la Facultad de Medicina de Bs. Aires, Jefe del Servicio Central de Radiología del Hospital Teodoro Alvarez, Miembro Fundador de la Sociedad Argentina de Radiología; Marcelo H. Moreau, Médico Agregado del Servicio Central de Radiología del Hospital Teodoro Alvarez, Miembro Titular de la Sociedad Argentina de Radiología, and Jorge E. Moreau, Médico Interno del Instituto Municipal de Radiología y Fisioterapia, Buenos Aires. Pp. 195, with 153 illustrations. Buenos Aires: Libreria Y Editorial "El Ateneo," 1941.

This relatively short monograph deals with the employment of oleoperitoneography in the study of the peritoneal cavity. This procedure is of greatest value in the diagnosis of peritoneal fluid, as even the lesser degrees of ascites, which may have escaped clinical notice, may be detected in this manner. Large abdominal cysts also may be recognized, as their roentgen appearance is characteristic during oleoperitoneography.

The technic consists of intraperitoneal injection of 3 cc. of iodized oil. Roentgenograms are then made with the patient supine, prone and erect.

The first seven chapters are devoted to a description of the peritoneal surfaces and the disposition and appearance of liquids and iodized oil in the peritoneal cavity in normal and in abnormal conditions. Experimental work on animals is included.

The remainder of the book consists of a series of observations in 40 clinical cases studied by the authors. Each case is illustrated by one or more excellent reproductions of roentgenograms. A short bibliography has been added.

Bronchiectasis: Pathogenesis, Pathology and Treatment. By James R. Liza, B.S., M.D., F.A.C.P., Pathologist, City Hospital, Welfare Island, New York, and Milton B. Rosenblatt, B.S., M.D., Associate Visiting Physician, City Hospital, Welfare Island, New York, Associate Attending Physician Montefiore Hospital. Cloth. Price, $4. Size of page 6¼ by 9½ inches. Pp. 190 plus an index, with 40 illustrations and 4 tables. New York: Oxford University Press, 1943.

This splendid monograph is the result of a painstaking study of 110 cases of bronchiectasis. A review of the anatomy and the physiology of the bronchi precedes the chapter devoted to theories of the genesis of bronchiectasis. Studies of the lesions encountered follow. The pathogenesis, the clinical aspects and the treatment are then considered in the order given.

The thesis elaborated throughout is that etiologically bronchiectasis is bacterial infection involving the bronchi and the adjacent parenchyma of the lung—it is not merely a dilatation of the bronchial tubes. In the vast majority of these cases it was a sequela of bronchopneumonia in childhood but in many it was produced by other infections, including those resulting from bronchial occlusion.

The book is printed on excellent paper; the illustrations are well selected and well reproduced. There is an extensive bibliography. The reviewer unhesitatingly recommends this work to all clinicians and students of medicine.

Primer of Allergy. By Warren T. Vaughn. Edition 2. Pp. 176, with 26 illustrations and 5 charts. Price, $1.75. St. Louis: C. V. Mosby Company, 1943.

One of the most serious problems of modern medicine is the question of education of the layman. How and to what extent can and should this be done? The little book under consideration exemplifies one method: snappy, slangy, epigrammatic discussion, illustrated by cartoons and slogans. For example, chapter 1, entitled "Learn to Live with Your Allergy," is headed by a drawing of a peculiarly imbecilic-looking white elephant led by a ridiculous little figure and labeled "Man's White Elephant." This sort of thing goes on throughout the book and is doubtless supposed to drive home the various points in an impressive way. The reviewer does not like this method. He feels that serious matters should be dealt with in a dignified way; that authors should elevate their audience and not play down to it. If these childish methods of instruction are really necessary, then there is indeed an intellectual decay among the citizens which demands decisive improvement of present educational methods.

A Text-Book of Pathology. By William Boyd. Edition 4. Pp. 1008, with 490 engravings and 29 colored plates. Price $10. Philadelphia: Lea & Febiger, 1943.

Dr. Boyd's justly popular treatise appears now in a new edition. Chapter 1, a brief philosophic discussion of the content of pathology, sets the stage, and the book then proceeds along conventional lines, dealing first with such general matters as degeneration, inflammation and tumors, and going on to the special diseases and organs. The writer's style is

simple and lucid; to the reviewer the real difficulty is that the subject has outgrown the bounds of any one reasonable volume. Just as a random example, the "pathology" of thiamine is dealt with in a single paragraph of some dozen lines. However, if the student knows all that Dr. Boyd has to tell him in this compressed treatise, he will be doing well enough.

Chemotherapy of Gonococcic Infection. By Russell D. Herrold. Price, not given. Pp. 137. St. Louis: The C. V. Mosby Company, 1943.

The actual substance of this little monograph, namely the part dealing with chemotherapy of gonococcic infections, occupies a relatively small part of the book; the remainder is to some extent unessential. Even in the sections on chemotherapy matters of common knowledge are reported at considerable length. The description of the systemic complications of gonococcic infections does not seem very adequate; arthritis is dealt with on one page; there is no discussion of general gonococcic sepsis or of the interesting cutaneous lesions. The reviewer disagrees sharply with the statement (p. 76) that removal of so-called chronic focal infections (teeth, tonsils, etc.) serves any particular purpose in gonococcic infections.

The March of Medicine: The New York Academy of Medical Lectures to the Laity, No. 7. Price, $2.50. Pp. 217, with 11 figures. New York: Columbia University Press, 1943.

The names of the writers, J. A. Miller, Tracy Putnam, A. A. Brill, Gesell, Jolliffe and Carlson, are enough to guarantee the high quality of the lectures. The value of medical presentations to the laity is always hard to assess; lecture audiences are notably of mixed intelligence. It seems worth while, therefore, that these discussions should appear in print, so that persons really interested can consider them at leisure. Tuberculosis, psychology and psychiatry, and nutrition make up the chief topics.

Renal Lithiasis. By Charles C. Higgins, M.D. Price, $3.00. Pp. 140, with 18 figures. Springfield, Ill.: Charles C Thomas, Publisher, 1943.

This little book, handsomely printed and illustrated, is an elaboration of the author's Beaumont Lecture on renal lithiasis. A considerable portion of the text is devoted to reports of the animal experiments on which the author bases his view that vitamin A deficiency plays a major role in the development of certain types of renal stone. A section on operative treatment comes next, and finally diet lists of foods high in acid ash and vitamins. There are a bibliography and an index.

The Neuromuscular Maturation of the Human Infant. By Myrtle B. McGraw. Pp. 140, with 28 figures. Price, $2. New York: Columbia University Press, 1943.

This scholarly little monograph deals in a highly technical manner with the details of development of neuromotor activities in the newborn. All the various reflexes, such as rolling and turning, receive meticulous consideration, and the whole subject is developed against a background of the general problem of behavior as well as neuroanatomy. This volume will surely have to be consulted by special workers in the field.

Flying Men and Medicine. By E. Osmun Barr. Price, $2.50. Pp. 270, with 10 drawings. New York and London: Funk & Wagnalls Company, 1943.

"Here is the story of aviation medicine told in simple English." This statement of the publisher, taken from the jacket, summarizes very well the contents of the book. The writing is excellent, and the material is comprehensive and soundly dealt with. The story is told in a vivid, but not sensational, manner. The layman interested in aviation should find it interesting reading. There is an index.

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A NOTE CONCERNING THE LONG NEGLECT OF AUENBRUGGER'S "INVENTUM NOVUM"

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In 1843 in a short introduction to Ungar's translation [1] of Auenbrugger's "Inventum novum," Josef Skoda in his brusque way declared that "to catalogue the reasons why Auenbrugger's discovery, which was so clearly set forth in his book, was not noticed by his contemporaries would be a useless task." A study of his book, he said, showed that Auenbrugger with the fullest right might be looked on as the founder of modern diagnosis.

Yet in spite of Skoda's pronouncement of a century ago the question has since that date been taken up more than once. Two papers deserve especial notice, one by Noltenius, the other by Neuburger. In 1908 Noltenius [2] published an exhaustive study of the problem of why the results of a scientific clinical investigation that had been carried on for seven years were gradually all but forgotten. In 1922 Neuburger's [3] critical monograph appeared, which, based largely on the work of Noltenius, would, as Sigerist [4] commented, seem to be the final word on the subject.

Noltenius and Neuburger, disregarding Skoda's pronouncement, offered several explanations of why Auenbrugger's work was ignored by some, ridiculed by others, or assailed as not new but old, a mere revamping of Hippocrates. The prevailing attitude of the medical mind of that day was philosophic and speculative; to employ manual help in diagnosis was banal and beneath the dignity of the high calling of the physician.[5] Then there were weak points in Auenbrugger's method. He sought for finer details than could be grasped by the beginner. Unfortunately he gave the impression that by percussion *alone* a diagnosis could be reached. Even his supporter Stoll (who in 1776 succeeded de Haen) acknowledged these failings.

One must recognize also that there were some imperfections in the technic that made it difficult for practitioners who lacked Auenbrugger's skill, patience and experience to be as sure of their results as he was. For example, he advised using one hand only. Percussion was to be made not over the bare skin; the chest was to be covered with cloth, e. g., the shirt. Or the hand might be encased in a glove. It can be readily understood how by such a procedure finer distinctions between tones might be missed, though they might be detected by the

1. Ungar, S.: Leopold Auenbrugger's Neue Erfindung, mittels des Anschlagens usw. Uebersetzung mit Vorwort von J. Skoda, Vienna, 1843. Later, a new edition appeared with a biographical sketch by Jadassohn, Berlin, 1908.

2. Noltenius, B.: Zur Geschichte der Percussion von ihrer Bekanntgabe durch Auenbrugger (1761) bis zu ihrer Wiederbelebung durch Corvisart (1808), Arch. f. Gesch. d. Med. **1**:329-350 and 403-428, 1908.

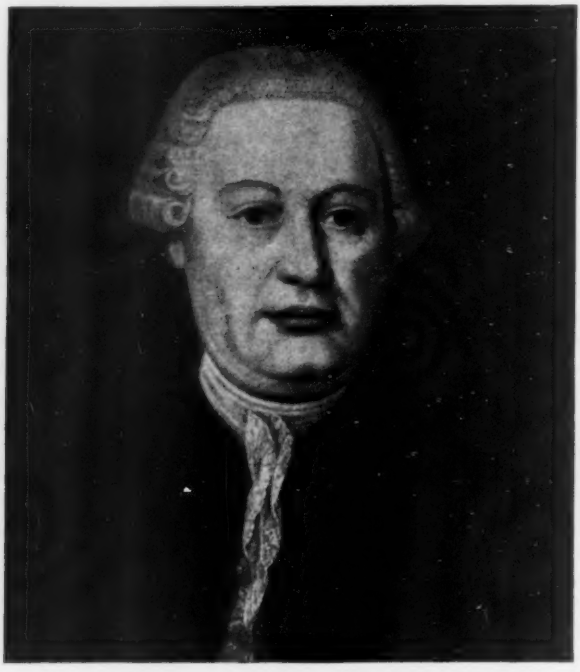
3. Neuburger, M.: Leopold Auenbrugger's Inventum Novum, Leipzig, Verlag von Josef Safar, 1922.

4. Sigerist, H. E.: Forbes' Translation of Auenbrugger, Baltimore, Johns Hopkins Press, 1936.

5. Neuburger,[3] p. 22.

musical ear of the discoverer, and the sense of resistance would be lost. Then, especially in the latter half of his book, there was vagueness, and even some error, in the presentation of his subject. All of these facts tended toward bewilderment rather than clarification in the mind of the reader.

That many failed to read the book at all or read it carelessly, confusing Auenbrugger's method with the Hippocratic succussion sound, is clearly brought out by Noltenius. In large measure, as Dock [6] emphasized, this was due to indolence; they were too lazy to read carefully, and they did not bother to translate accurately. And Neuburger was probably right in his caustic statement that the number of



LEOPOLD AUENBRUGGER, 1722–1809

Fig. 1.—Leopold Auenbrugger (from Sigerist, H. E.: The Great Doctors, New York, W. W. Norton & Company, Inc., 1933, facing p. 240).

those who were not able to hear when they percussed was decidedly smaller than the number who did not wish to hear. They were against the revolutionary ideas of the young upstart.

Finally, Auenbrugger's Latin was not always clear, a point brought out by Ungar,[1] which will be taken up later.

In offering my views there is no intent to dispute the claim that Auenbrugger was a pioneer in modern diagnosis, at least as it concerns physical diagnosis of

6. Dock, G.: Leopold Auenbrugger and the History of Percussion, Michigan Alumnus, November 1898.

diseases of the chest, nor in any way to belittle the importance to medicine of his remarkable volume, "the little book so small, so terse, so wonderful," as Weir Mitchell [7] termed it. It was largely because of the stimulus given by the "Inventum novum" that the work of Corvisart, who revived Auenbrugger (1808) and generously gave him full credit for his discovery, as well as the work of Laennec, of Skoda himself and of others made Auenbrugger's place in the hall of fame forever secure.

The long neglect of Auenbrugger is not a unique occurrence. While the worth of some epoch-making medical discoveries has been promptly recognized, delay in acknowledging the merit of others has led to tedious, perhaps ill tempered discussion and to resentful reaction on the part of the discoverer and his friends. Some, like the sensitive Semmelweiss, after pleading in vain, after brooding until worn out, have finally broken down. Had Semmelweiss flared up with a violent outburst of angry invective, the result might have been less tragic. When Scotch reviewers unjustly attack it may be better to fight back as did Byron than to wilt as did the hypersensitive Keats.

Some, however, did not break down. Vesalius bitterly resented the criticism of his contemporaries. In a fit of anger he burned his books and manuscripts, gave up teaching and, shaking the dust of Padua from his feet, left that city to become the court physician of the Emperor Charles V. Nor did the peppery Harvey suffer in silence. In 1649, in his second disquisition to Riolan of Paris, he referred to contemporary critics of his "De motu" as detractors and mummers who were unworthy of an answer. "Let them consume on their own ill-nature. They will scarcely find many well-disposed readers, I imagine, nor does God give that which is most excellent, and chiefly to be desired—wisdom—to the wicked. Let them go on railing, I say, until they are weary, if not ashamed." [8]

Yet Auenbrugger's action was strangely different from that of Semmelweiss, Vesalius and Harvey. He did not wait to be attacked; he *anticipated* such action. He expressed beforehand the utmost contempt for those who, he said, *would* attack him; declared he would not deign to answer them. In general he seems to have kept this vow.

That the forty years' neglect of Auenbrugger was in large measure due to the causes so thoroughly considered by Noltenius and Neuburger is clear. Yet, in addition, commentators have generally charged that much of the onus for this unfortunate and tragic occurrence must be borne by the two leaders of Viennese medicine of that time, van Swieten and de Haen. Had these two men been friendly, had they publicly endorsed Auenbrugger, all would have been well, one is told. Instead, they preserved an "icy silence." They ignored the industrious young scientist, though they were familiar with his work, for it was carried on largely in their wards.

Auenbrugger has been all but canonized by his admirers. The purpose of this paper is to offer the rather heterodox suggestion—I dare not use a stronger term, like "claim"—that the fault may have lain, much more than is generally recognized, in Auenbrugger himself, in his peculiar personality. Perhaps, after all, he was human, with the frailties of ordinary human beings.

For some reason he did not always get along well with his fellow workers in the wards. Is it not possible that while working in the Spanish Hospital, using many patients that had been loaned him through the courtesy of de Haen and van Swieten, his attitude toward his associates and his superiors gave offense?

7. Mitchell, S. W.: Early History of Instrumental Precision in Medicine, New Haven, Tuttle, Morehouse & Taylor, 1892, p. 24.

8. Powers, D'A.: William Harvey, London, T. F. Unwin, 1897, p. 226.

g: Van Swieten.

GERHARD VAN SWIETEN, 1700-1772

A De Haen

ANTON DE HAEN, 1704-1776

Fig. 2.—Gerhard van Swieten and Anton de Haen (from Sigerist, facing p. 209).

Most commentators have referred to Auenbrugger as a modest, unassuming man who was a martyr to the ignorance and the ill natured opposition of his contemporaries de Haen and van Swieten. Ungar in his preface to his translation of the "Inventum novum," said that in "1761 the book appeared timidly and modestly" (*zaghaft und bescheiden*). But is this the spirit shown in Auenbrugger's preface? Was he not a little toplofty, "biggity" as Uncle Remus would say, when he declared that after seven years of study he *knew* (italics mine) that his results were correct? Readers, he said, would of course be influenced as they had been in the case of other investigators, by envy, malice, hatred, detraction and calumny. He expected to be vilified. But he did not propose to waste any effort in the future to reply to criticism or to advance further proof. He seems to have been saying: "Take it or not; I am indifferent as to what you do. I admit that much remains to be discovered, but—let others do the work, I'm through." This failure of Auenbrugger to follow up the rich lead he had discovered was aptly referred to by Dock [9] as strange and unexplained.

Now could the two leaders of the Vienna school be expected to bestow an approving pat on the back of this young man of 39 years who assumed such a lofty, almost defiant, pose? Was it not asking too much of them? The tempestuous 57 year old de Haen, true to form, opposed the innovation because, forsooth, as Neuburger [10] has said, he was not its author. Van Swieten, then 61, better poised and peace loving, though he had been referred to by Auenbrugger in complimentary terms as the illustrious Baron van Swieten, quietly ignored the remarks of his pupil that, to say the least, were tactless. Possibly van Swieten may have said to his colleague de Haen, as he once wrote him on another occasion and on another topic, "What's the sense of all this row? Quiet down. I never court a fight." [11] That they did ignore him is shown by the fact, vouched for by Noltenius and confirmed by Clar,[12] that in the voluminous writings of these two men—de Haen in 1769 had fifteen volumes to his credit—not one reference to Auenbrugger and his percussion is to be found. Ungar said van Swieten may perhaps have given him the *slightest* notice, thus damning him with faint praise. Noltenius,[13] however, said that van Swieten's "Commentaries on Boerhaave's Aphorisms," though discussing hydrops and empyema of the chest, made no mention of percussion. May not Auenbrugger's attitude explain in part the indifferent or unfriendly reception given by these men to his book?

As an extenuating circumstance that may help explain the resentful behavior of Auenbrugger one may surmise, as did Noltenius, that Auenbrugger had been subjected to criticism and ridicule by skeptical physicians who saw him at work day after day in the wards, going through a performance that to them seemed nonsensical. After seven long years of such unpleasant treatment it can be understood how all this "got under his skin," how he became exasperated, irritable, rebellious. One may surmise also that Auenbrugger was unaware of the state of his own mind at the time he wrote. He may have harbored in his subcon-

9. Dock, G.: Roziere de la Chassagne, and the Early History of Percussion of the Thorax, Ann. M. Hist. **7**:438-450, 1935.

10. Neuburger,[3] p. 26.

11. See Ebstein, E.: *Aerzte-Briefe* aus vier Jahrhunderten, Berlin, Julius Springer, 1920, pp. 18-24. Strangely, too, in this same letter, written Sept. 10, 1761, he also said: "I am not ashamed to learn from a young physician." Though there is no warrant for assuming that van Swieten had Auenbrugger in mind when he wrote this, it is a striking coincidence that the preface to Auenbrugger's book was dated only a few months before this time, Dec. 31, 1760. The volume itself appeared early in 1761.

12. Clar: Leopold Auenbrugger, der Erfinder der Percussion des Brustkorbes, geb. zu Graz 1723, gest. zu Wien 1809, und sein Inventum novum, Graz, Leuschner u. Lubensky, 1867.

13. Noltenius,[2] 338.

scious stratum a tenseness that was close to the breaking point. When the book had been published, when this tenseness was relieved, when he was sadly disillusioned as to hoped-for praise by van Swieten, he may have sorrowfully realized what he had done and how he had given offense.

Early in 1762 he manifested resentment when he referred to the jealousy and misunderstanding of colleagues. In the preface to a book dealing with the treatment of mania in men, "Experimentum nascens de remedio specifico . . . ," he said that "the history of my last patient is incomplete because today—January 14, 1762—my subordinate in rank who later became my successor, induced by clandestine motives, to my surprise and without telling me about it, discharged the patient from the hospital." Also, in the foreword to the book he unquestionably referred to himself when he quoted "rarus enim propheta in patria." Further, in 1776 in a letter to Haller [14] which accompanied a gift copy of the book "Experimentum nascens," he apologized for certain imperfections, and said

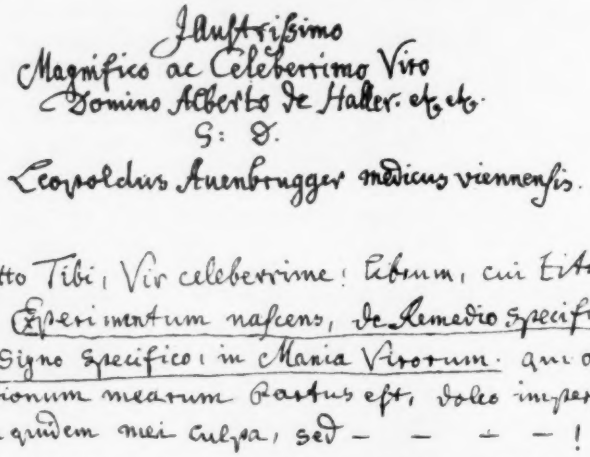


Fig. 3.—Facsimile of the first paragraph of Auenbrugger's letter to Haller (from Neuburger,[3] facing p. 24).

he trusted they might be overlooked, for it was not his fault that they were there: "Non quidem mea culpa est, sed . . . !" One can only wonder what is meant by the "sed . . . !"

It is not easy for one today to interpret correctly what may have been the true intent of something written nearly two centuries ago. Correct interpretation demands a retrojection of the commentator into the past so that so far as possible he realizes conditions as they were at that time. Contemporaries are to be judged by the yardstick of their time and not by that of today, as Neuburger put it. It is because this cannot be satisfactorily done that it may be unfair even to hint that when in his preface to the "Inventum novum" Auenbrugger said, "I prefer to express myself in a few words," in his own mind he underscored the word "I." Could it be that there was—perhaps unintentionally—a satirical

14. Neuburger's Monograph [3] (facing page 24) has a photostatic copy of the autograph letter, as well as one of a letter of sympathy to Haller, whose son had died in 1778.

sting concealed here? Or may, possibly, de Haen and van Swieten, those experts in prodigal wordiness, have felt that there was a covert reference to themselves? [15]

The period 1761 to 1776, the year when de Haen died, the period in which the method of percussion was treated partly by dead silence, partly by scorn, was not an entirely happy one for Auenbrugger, as quotations from his writings have shown. Yet he was by no means entirely unhappy. He was busy with practice and was called in consultation by physicians and surgeons, especially in cases of disease of the chest. He was popular as a practitioner, noted for his kindness to the poor, happy in his home life and in his love of music, a welcome guest in social circles. "A grave, contented, music-loving German" Weir Mitchell [16] called him. Honors came to him later. In 1784 he was elevated by the Emperor Joseph to the nobility as "Edler von Auenbrugger." While his last years were made sorrowful by impaired eyesight and by the loss of his wife, in 1807, it surely must have cheered the heart of the old man to know that, owing to Corvisart, his work was at last accorded the world praise that was long overdue. He died May 18, 1809, in his eighty-seventh year.

AUENBRUGGER'S LATIN

The terseness of Auenbrugger's Latin and its predominant clarity have justly excited favorable comment. Yet, in places, and in a measure because of this terseness, one has difficulty in getting the exact meaning. Ungar [1] referred to his Latin as "etwas dunkel. . . ." "The peculiarity of the author's style, the frequent ambiguity of expression, the apparent contradiction in places of statements found elsewhere, the incompleteness of the terminology have made the interpretation difficult."

I omit as not germane to the question discussed in this paper all consideration of the critical study made by Ungar of various portions of the main body of the text of the "Inventum novum." Attention is directed to the preface and especially to the ninth sentence, which is also the ninth paragraph. That the meaning of this paragraph is not clear is shown by the fact that it has been translated by different commentators in several ways. It reads as follows:

Et haec erat ratio, cur cum signis quieverim, atque etiam in his, ad inevitabilem causarum quarundam enumerationem, quae ad illustrandas observationes meas conferre poterant, confugerim ad commentaria Illustrissimi L. Baronis van Swieten, quoniam in his, quid quid ab observatore Homine desiderari unquam potest, absolutum invenitur.

The English translation (Forbes) reads: "Owing to this acknowledged imperfection, it will be seen, that, in my difficulties, I have had recourse to the Commentaries," etc. In the French (Corvisart) it is interpreted to mean: "This is the reason why when I felt the lack of signs," etc. ("lorsque je manquai de signes"). Ungar said Corvisart's translation of "et haec ratio" is forced and not in agreement with the preceding sentence. The translation of "quiescere" is contrary to "every Latinity," he declared. The German translation, as it seems to me, comes nearer to the meaning; it interprets "quiescere" as "to be satisfied with" ("es . . . bei . . . bewenden lassen").

15. I may add that much later, in 1867, Clar of Graz, who though he defended Auenbrugger yet made critical, not always laudatory, comments on his work, was guilty of tremendous long-windedness, as witness one sentence of about 550 words covering a page and a half. The only other writer whom I have run across who compares with him in this respect is Friedrich Kreysig (Herrick, J. B.: A Short History of Cardiology, Springfield, Ill., Charles C Thomas, Publisher, 1942, p. 81).

16. Mitchell,[7] p. 24.

In my perplexity over the proper translation of this sentence I appealed for help to my friend Payson S. Wild, of Chicago, well known as an expert classical scholar. I am grateful to him for his opinion in the matter. He believes that "quieverim," as well as "confugerim," depends not on "cum" but on "cur." "Cum" is a preposition followed by "signis"; it really goes with, or is a part of, "quieverim." Facciolati and Forcellini, in their "Totius Latinitatis Lexicon," have cited examples from classical Latin in which—*per synechdochem*—"quiescere" is used as the equivalent of "omittere or desinere," translated in English "to give over," "to leave off." Auenbrugger seems to have followed a German usage—much like the use of *aufhören*. He meant to say he "broke off with" the signs, stopped considering or experimenting with these signs. The sentence may then be translated: "And this was the reason why I stopped experimenting with these signs, and why also, as an aid in the necessary listing of certain causes that could assist in making clear my observations, I had recourse to commentaries of the most illustrious Baron van Swieten, since in these whatever is needed by the observant individual is sure to be found."

He continued in the next paragraph: "I thus avoided the need of prolix writing and also laid a most secure foundation on which the rudiments of my discovery would more creditably rest."

SUMMARY

That the "Inventum novum" was all but forgotten until revived by Corvisart in 1809 was largely due, as shown by others, to several factors. Auenbrugger gave the wrong impression, viz., that by percussion alone a diagnosis could be made. His technic was not perfect—e. g., he used one hand only and that often covered by a glove—so that less skilled physicians failed to get the hoped-for results. Many who read his book carelessly, if at all, thought he was merely revamping the old Hippocratic sound. The meaning of his Latin was at times obscure. Especially, a large part of the blame has been attributed to the "icy silence" of his seniors, de Haen and van Swieten, in whose wards he worked.

In this note the question is raised whether Auenbrugger's own personality may not have had much to do with alienating de Haen and van Swieten. There is presented evidence that he had difficulty in getting along with other workers in the wards. In his preface his words reveal a toplofty or defiant attitude; he knew he was right; though much remained to be done in perfecting the method, he was through, others must do it; he expected to be vilified as other contributors to science had been but he would not deign to answer criticism of any kind. All this may have given offense to these Viennese leaders. That he was keenly disappointed by the action of his chief, van Swieten, is clear. That he was tensely nervous and irritable is highly probable. Even long after 1761 his resentment is shown by excerpts from letters. A critical study of a paragraph from his preface is added as an attempt to clear some of the obscurity of his Latin.

In offering this rather heterodox explanation I wish to declare my admiration for Auenbrugger's talent as an original investigator as well as for the content and terse Euclidean style of the "Inventum novum." His place in the hall of fame is forever secure.

SCLERODERMA HEART DISEASE

WITH A CONSIDERATION OF CERTAIN OTHER VISCERAL MANIFESTATIONS OF SCLERODERMA

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It is the purpose of this paper to call attention to the involvement of organs other than the skin in the course of scleroderma and to discuss particularly the clinical and the pathologic changes resulting from myocardial lesions associated with this condition.

The physician frequently encounters patients with heart disease which does not fit into any of the various categories usually listed in textbooks of medicine.[1] Unless particular attention is paid to the establishment of the etiologic factors underlying the condition one is likely to miss the significance of certain rarer forms of generalized disease which may lead to myocardial failure. It is easier to conclude that a given patient suffers from an unusual manifestation of arteriosclerotic, hypertensive, rheumatic, syphilitic or congenital heart disease than it is to establish the association of myocardial changes with some less familiar condition which may affect the heart. One of these less familiar conditions is scleroderma.

Because of the forcing of certain cases into the better recognized forms of heart disease the progress of knowledge regarding etiologic classification has been handicapped. Accurate etiologic classification is of practical, as well as of theoretic, importance, because many of the rarer forms of heart disease are amenable to specific therapy. Although the incidence of any one of these less common forms of heart disease is not great, the group as a whole comprises an appreciable percentage of the instances of cardiac disease encountered in medical practice. The observation that generalized scleroderma was one of the "not well recognized" causes of heart disease led to the present study.

The causation of the generalized form of scleroderma is not known.[2] It occurs in females about twice as often as in males and most frequently in persons in the fourth and the fifth decade, but it can occur at any period from infancy to old age. The course is extremely variable; the onset may be insidious with many years required for its full development, or the disease may appear and progress

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† This paper represents an expansion of material collected by Dr. Weiss before his death on Jan. 30, 1942. Dr. Weiss presented this material in part at a meeting of the New England Heart Association in Boston on Dec. 15, 1941.

1. Weiss, S.: Diseases of the Heart and the Aorta Which Are Not Well Recognized, M. Clin. North America **23**:1323 (Sept.) 1939.

2. Burch, G. E.: Scleroderma: Etiology and Abnormal Physiology, New Orleans M. & S. J. **92**:12 (July) 1939.

to a fatal termination in a few weeks.[3] The early stages of the disease may be characterized by the presence of slight edema, induration and inflammatory changes in the skin, to be followed later by the more characteristic, tight, "hide-bound" skin, usually deeply pigmented, but with occasional areas of pigment loss. The skin may vary in color from ivory to darke bronze, like that seen in hypoadrenalism with pigmentation. The skin of the extremities and the face is commonly involved, but that of the entire body is also frequently affected. In many cases Raynaud's syndrome occurs either before, simultaneously with or after the onset of scleroderma. There is frequently a history of symptoms referable to joints, and a diagnosis of rheumatoid arthritis may be made before the scleroderma becomes obvious. Atrophy of the skeletal muscles often occurs. This happens not only under the sclerodermatous skin but distant from it, probably because of disuse. There may be slight fever, malaise and constitutional symptoms.

Various laboratory procedures have not given consistently abnormal results. There may be slight anemia. The basal metabolic rate usually is within normal limits but may be moderately elevated or, more frequently, depressed. Roentgen examination of the involved parts may show decalcification of bone or even loss of bony substance in the terminal phalanges, and at times there may be calcified areas in the skin.

When first described, scleroderma was regarded as a disease restricted to the skin, but later writers on the subject have described manifestations in other organs. It is now well known that the disease may affect the lungs, the endocrine glands and the gastrointestinal tract.[4] Although pathologic changes in the heart have been reported in a few cases,[5] cardiac symptoms during the course of scleroderma have rarely been described. The following cases are reported because they all have aspects which suggest the presence of heart disease of an unusual type in patients with generalized scleroderma. Other instances of generalized scleroderma have been encountered in which there has been suggestive evidence of myocardial involvement. Because our data on the latter cases are incomplete, they are not recorded here.

REPORT OF CASES

CASE 1.—M. W., a housewife aged *27*, was admitted to Peter Bent Brigham Hospital in 1940.

History.—Six years before admission she noted that her hands were frequently cold and clammy, and in August 1934 her hands turned a "waxy white" while she was swimming. At this time she also had mild aching in both wrists. The symptoms became more frequent and severe, and in October 1935 right and left cervicothoracic sympathectomies were performed. Although there was temporary improvement, the symptoms returned and were accompanied later by pain and cyanosis of the fingers. Three years before admission persistent deformity of the hands first developed, with flexion contractures and occasional swelling. About one and a half years before entry she noted pigmentation of her hands, which she though at first to be just "tan." At the same time a few areas of depigmentation appeared in the skin. The skin of her face, hands and feet became tight and shiny; later the skin of the entire body became involved. From time to time small ulcerated areas would appear on her finger tips and over bony prominences.

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3. MacCallum, W. G.: Acute Diffuse Scleroderma, Tr. A. Am. Physicians **41**:190, 1926.

4. (*a*) Matsui, S.: Ueber die Pathologie und Pathogenese von Sclerodermia universalis, Mitt. a. d. med. Fak. d. k. Univ. zu Tokyo **31**:55, 1924. (*b*) Linenthal, H., and Talkov, R.: Pulmonary Fibrosis in Raynaud's Disease, New England J. Med. **224**:682 (April 17) 1941. (*c*) Ochsner, A., and DeBakey, M.: Scleroderma: Surgical Considerations, New Orleans M. & S. J. **92**:24 (July) 1939.

5. (*a*) Brock, W. G.: Dermatomyositis and Diffuse Scleroderma, Arch. Dermat. & Syph. **30**:227 (Aug.) 1934. (*b*) Matsui.[4a]

For about one year prior to admission the patient experienced gradually increasing dyspnea, which became quite severe during the two or three months before admission. Associated with this she had moderate swelling of the ankles, and for five or six weeks her face was swollen on arising in the morning. In the month prior to admission she became orthopneic and spent several nights sitting up in a chair. She also had a dry cough and occasionally woke up at night with a severe coughing spell and dyspnea. At such times she would frequently cough up white frothy sputum.

A year or so before admission she began having "heartburn" and would often have a feeling of substernal fulness soon after eating. On rare occasions this was accompanied by vomiting. There were no other gastrointestinal symptoms. A review of each system failed to reveal any other complaints.

Physical Examination.—On admission to the hospital the patient was well developed but poorly nourished. The skin of the entire body had a "tanned" appearance and was tight, shiny and inelastic. The changes were most marked about the face, arms and hands. There were several small areas of nonpigmented skin. There was moderate thinning of the hair. The face was expressionless; the mouth was small and could be opened to a limited extent only. The retinal vessels were not abnormal. The voice was rather hoarse. The

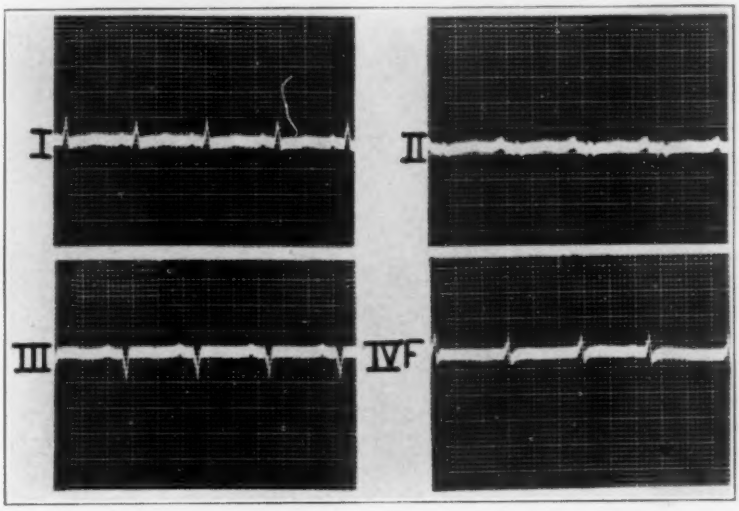

Fig. 1 (case 1).—An electrocardiogram.

veins of the neck were distended, and the neck was slightly stiff. Examination of the lungs revealed slight dulness and moist rales at both bases posteriorly. The heart was moderately enlarged to the left. The rate was rapid and regular except for an occasional premature beat. The sounds were of good quality, and there was a slight apical systolic murmur with a protodiastolic gallop sound. The pulmonic and the aortic second sounds were of equal intensity. The arterial pressure was 140 systolic and 100 diastolic. The abdomen was rather full and tense, but examination failed to reveal definite evidence of fluid. The edge of the liver was not felt, but there were dulness and tenderness in the right upper quadrant of the abdomen. The spleen could be felt to descend on deep inspiration. There was moderate edema of the sacral region and the ankles.

Laboratory Examination.—The hemoglobin content of the blood and the red and the white cell count were normal. The specific gravity of routine specimens of urine ranged as high as 1.022. All samples contained albumin (3 plus), and two contained occasional red and white cells. The total serum protein was 6.7 Gm. per hundred cubic centimeters, with 3.3 Gm. of albumin and 3.4 Gm. of globulin. The serum per hundred cubic centimeters contained 152 mg. of cholesterol, 10.2 mg. of calcium and 4.0 mg of phosphorus. There was 48 per cent excretion of phenolsulphonphthalein in two hours. Vital capacity was 1,100 cc. The circulation time

with sodium cyanide (arm to carotid sinus) was forty-two seconds. The venous pressure in the antecubital vein was 250 mm. of water, the normal range by the method used being 50 to 150 mm. of water. Pericardial fluid (obtained at postmortem examination) was clear yellow, with a specific gravity of 1.017 and a total protein content of 3.7 Gm. per hundred cubic centimeters. Electrocardiograms showed low electromotive force, slight left axis deviation, low T waves and premature auricular and ventricular beats (fig. 1). Roentgen examination revealed marked cardiac enlargement, both to the right and to the left (fig. 2). The heart was triangular in shape and had a wide base. The amplitude of the beat was diminished. The findings suggested the diagnosis of a pericardial effusion. There were moderate pulmonary congestion and fluid in both pleural cavities. Roentgenograms of the hands and wrists showed

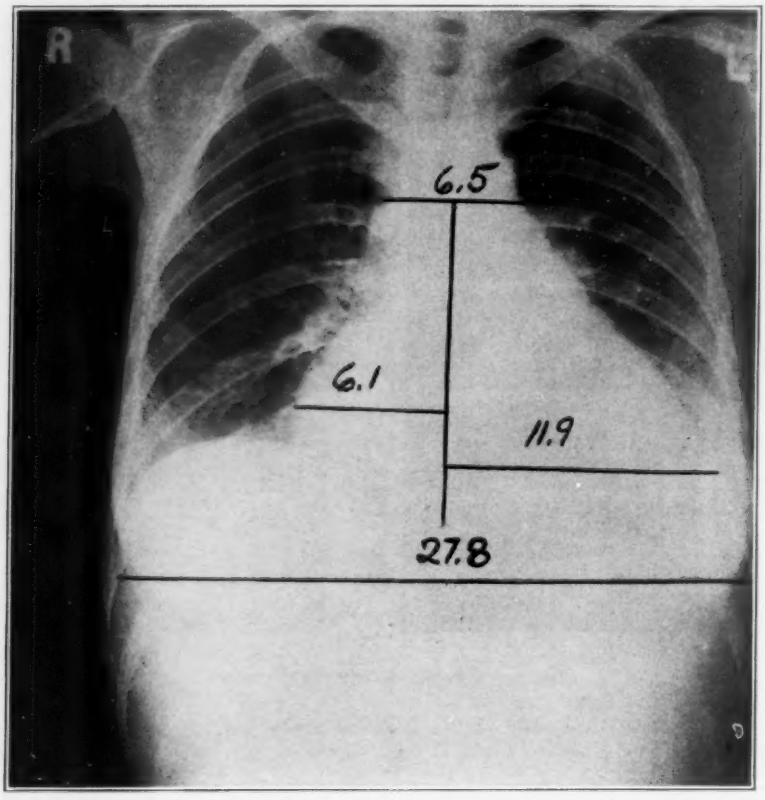

Fig. 2 (case 1).—A roentgenogram of the chest. The heart is greatly enlarged. It is triangular, with a broad base.

definite atrophic changes, with partial loss of the terminal phalanges, more marked on the right hand.

Course of Illness.—The patient's temperature remained normal throughout her stay in the hospital. The pulse rate ranged between 80 and 110 beats per minute. She continued to have respiratory difficulty despite therapy with digitalis, ammonium chloride and mercupurin. On the eleventh day in the hospital, while sitting on the edge of her bed eating lunch, she suddenly fell back on the bed, rapidly became unconscious and cyanotic, gasped a few times and died.

Anatomic Diagnoses.—The anatomic diagnoses included scleroderma; myocardial cicatrization; hydropericardium (340 cc.); bilateral hydrothorax; ascites; generalized edema; chronic passive congestion of the liver; splenomegaly (weight of spleen, 280 Gm.); atrophy

of the thyroid; bilateral degeneration of the crura of diaphragm and of the second and the third intercostal muscle.

Autopsy.—The skin in all regions was smooth, thick and leathery in texture. Only with great difficulty could the skin be lifted from the underlying tissues, and no wrinkling resulted from this procedure. Over the lower portions of the abdomen and about the neck, wrists and lower parts of the forearms the skin was dark brown. This was in contrast to areas which were pure white, distributed in patches over the abdomen and in longitudinal linear streaks in the heavily pigmented regions of the neck and wrists. The rest of the skin was white, without areas of deep pigmentation. Because of the induration of the skin, the fingers were fixed in a position of flexion. There were small ulcerated lesions on the second and the fourth finger of the right hand, on the right knee and on both internal malleoli. The distribution of body hair was normal. On external examination subcutaneous edema was demonstrated in both legs, over the sacrum and in the labia majora.

Fig. 3 (case 1).—The posterior aspect of the heart. The heart is globular. There are numerous scars in the walls of both ventricles, for the most part linear in distribution.

In making the primary incision it was noted that there was marked edema of all subcutaneous tissues, the edema being apparent to external examination only where maximal because of the induration of the skin. There was no subcutaneous fat. The second and third intercostal muscle on either side was grayish pink and reduced in size. Other voluntary muscles were pale but normal in contour.

The peritoneal cavity contained 600 cc. of clear, yellow fluid. The crura of the diaphragm on both sides were slightly thinner and considerably paler than the central portions.

The left pleural cavity contained 750 cc. of yellow fluid and the right one 900 cc. There were a few easily broken adhesions about the apex of each lung. The pleural surfaces were smooth, moist and glistening. Examination of the mediastinum showed nothing abnormal.

The parietal pericardium was markedly edematous and gelatinous in appearance. Three hundred and forty cubic centimeters of yellow fluid was present in the pericardial cavity. The serous surfaces were free from exudate.

The heart weighed 300 Gm. and was globular in shape. A moderate amount of pale epicardial fat was distributed chiefly along the course of the coronary vessels. Over the anterior surface of the left ventricle, just to the left of the interventricular septum, there were numerous linear white areas involving both the epicardium and the superficial portions of the myo-

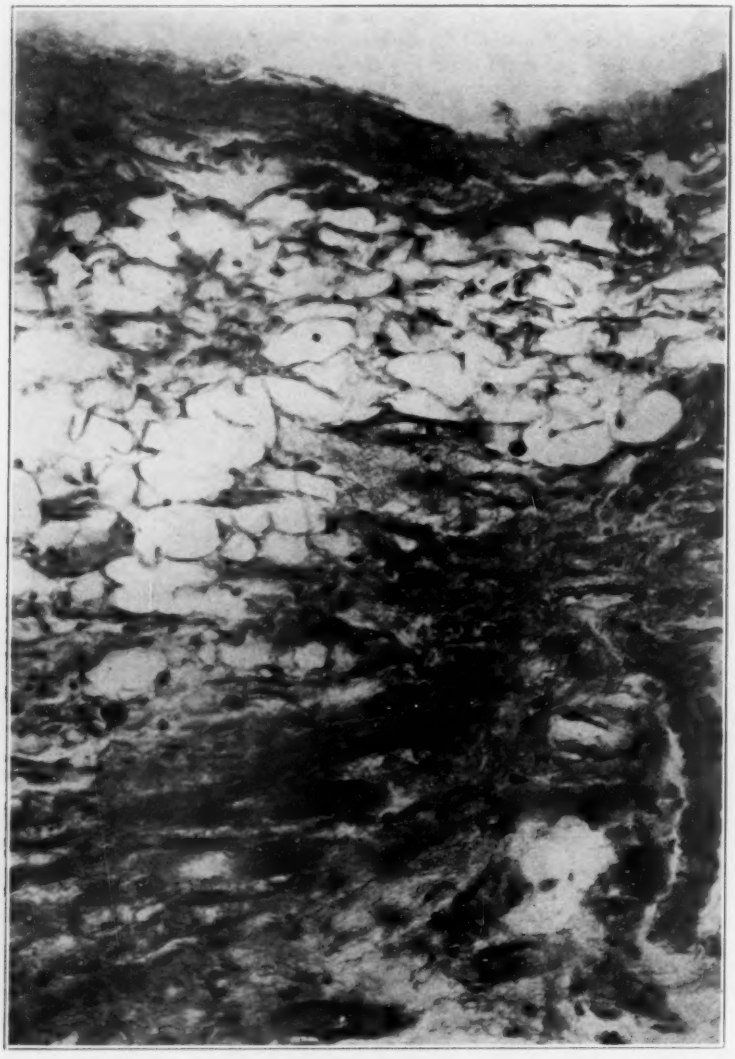

Fig. 4 (case 1).—A scar in the superficial part of the myocardium with extension into the subepicardial fat. The connective tissue beneath the mesothelial layer is increased in amount. Eosin–methylene blue stain; × 300.

cardium. These areas measured 1 to 2 cm. in length. They were somewhat firmer than the intervening tissue. On the posterior aspect of the heart (fig. 3) similar white areas were present in even greater numbers. There was one white region 2.5 cm. in diameter correspond-

ing to the points of origin of the posterior papillary muscles. This area was puckered, somewhat concave and firm in texture. The cut surface of the myocardium was paler than usual, with irregular firm white streaks among the bundles of muscle. All valves were normal. The coronary arteries were not thickened or occluded. Their intimal surfaces were entirely free from atheromatous plaques.

The right lung weighed 270 Gm.; the left one, 230 Gm. There was normal crepitancy in all lobes. Surfaces made by cutting were pale pink; a small amount of pink fluid was expressed by pressure. The hilar lymph nodes were normal.

The spleen weighed 280 Gm. It was firm in consistency, and the capsule was not wrinkled. The color of the cut surface was deep red, traversed by firm white lines. Thin sections held their shape perfectly.

Fig. 5 (case 1).—An area of scarring within the myocardium. The scar is composed of collagenous tissue rich in fibroblasts and in capillaries. A few muscle fibers remain well up within the lesion. Eosin–methylene blue stain; × 300.

The liver weighed 1,380 Gm. The capsule was not thickened. The organ was firm in consistency and deep red in color. Externally, as well as in cross sections, there was conspicuous lobular mottling, consisting of deep purple central zones surrounded by pale yellow hepatic parenchyma.

The thyroid weighed 22 Gm. It was uniformly firm in consistency. Little colloid could be seen in the deep red, meaty surface exposed by cutting.

The aorta was elastic and free from atheroma.

The alimentary tract, pancreas, gallbladder, kidneys, adrenals, uterus, ovaries, venae cavae, ribs, vertebrae, breasts, parathyroids, brain, pituitary and spinal cord did not show any significant changes on gross and microscopic study.

Microscopic Examination.—Heart: Sections taken from the regions in which white streaks were noted grossly showed areas of fibrosis unusual in character. These areas were most numerous just beneath the epicardium, but they also were encountered in midmyocardium and under the endocardium. Medium-sized arteries were often included in the areas of fibrosis, but the fibrosis was not always perivascular in position. These arteries showed little evidence of intimal thickening. There was no medial degeneration or atheromatous deposits.

The connective tissue in the areas of fibrosis was composed of delicate collagen fibers with numerous fibroblasts (fig. 5). From place to place, fat cells, singly or in groups, were encountered in the connective tissue (fig. 7). There were no hemosiderin deposits or infil-

Fig. 6 (case 1).—A photomicrograph showing the relation of a myocardial lesion to the surrounding musculature. The edges of the scar are irregular, and its connective tissue blends with that of the adjacent myocardium. Scattered muscle fibers persist within the lesion. Eosin-methylene blue stain; × 150.

tration with inflammatory cells. Occasional myocardial fibers persisted within the areas of fibrosis (fig. 6). Many of these fibers were morphologically normal but were completely isolated by connective tissue. Other isolated fibers showed various stages of degeneration. The scars were unusually vascular (fig. 5), numerous capillaries being found among the connective tissue fibers. They were thin walled and engorged with blood, often markedly so. The tissues of the scars, in consequence, bore more resemblance to granulation tissue than to scars due to arteriosclerosis or to old myocardial infarction. The process was regarded as one of gradual replacement of muscle fibers by fibrous tissue. The atrophy of muscle fibers appeared to be the result of compression and strangulation by the overgrowth of col-

lagenous tissue rather than a primary process to which the proliferation of connective tissue might have been a response. No areas of recent infarction were encountered.

In sections which did not contain focal areas of fibrosis, there was a diffuse broadening of the bands of the myocardial connective tissue. The fibrous tissue was edematous, delicately fibrillar and rather cellular in character. Capillaries were abundant and conspicuously engorged. The myocardial fibers in these areas were normal in appearance.

The endocardium was normal in thickness in many areas. Elsewhere, however, it was greatly thickened by an increase of fibrous tissue, which blended with the connective tissue of the underlying myocardium.

The epicardial surfaces showed no evidence of inflammatory change. In several places, however, there were focal areas of lymphocytic infiltration in the epicardial fat. From place

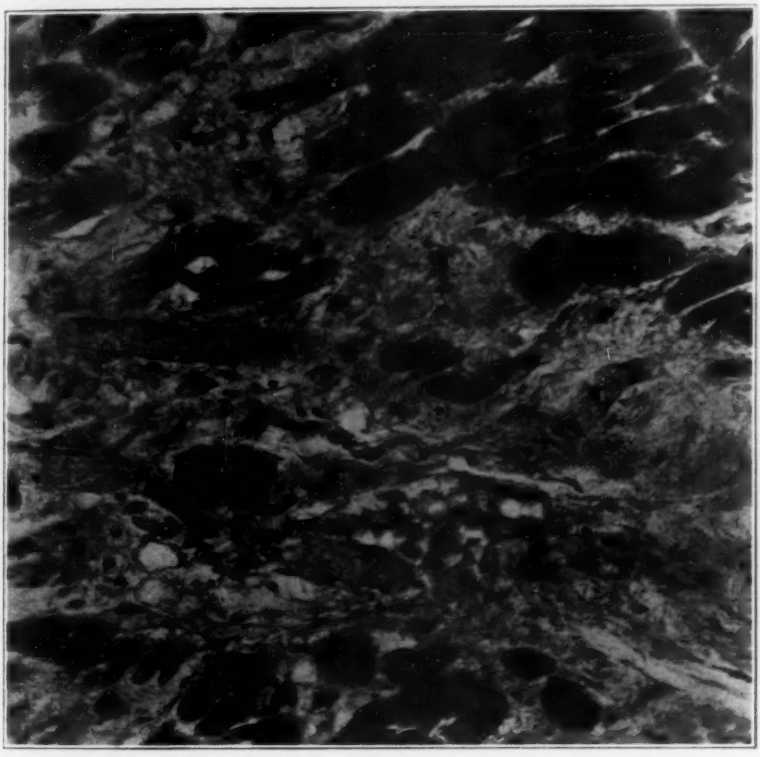

Fig. 7 (case 1).—A portion of a myocardial lesion containing a group of shrunken fat cells and engorged capillaries. Eosin-methylene blue stain; × 300.

to place, areas of fibrous tissue, similar to that in the myocardium, were found in the epicardial fat. These were directly continuous with scars in the myocardium and seemed to be due to the spread of a process originating within the musculature (fig. 4). The coronary arteries presented little intimal thickening, and no atheromatous deposits were encountered.

Lungs: In most areas the only abnormality was vascular congestion and a slight increase in the perivascular connective tissue. There were a few regions in which the connective tissue of alveolar walls and interlobular septums was strikingly increased (figs. 8 and 9). In these regions, vascular engorgement was marked. Large numbers of mononuclear cells were encountered in the alveoli, some of which contained hemosiderin. Many red cells were present in these alveoli, but polymorphonuclear leukocytes were not encountered. The bronchi

were normal. There was moderate thickening of the pleura by dense connective tissue. The walls of blood vessels were free from sclerotic changes.

Spleen: The splenic sinusoids were much engorged, and the red pulp was largely depleted of lymphocytes. There was a considerable increase of the connective tissue among the sinuses. In contrast, the malpighian corpuscles were discrete, large and numerous. Moderate thickening and hyalinization of the arterioles and of the intima of larger arteries were noted.

Liver: In the central zones of lobules, especially in the subcapsular region, the sinusoids were markedly engorged, with destruction of intervening liver cord cells. The strands of endothelial cells remained, but there was no definite increase in connective tissue. The peripheral portions of the lobules were well preserved.

Thyroid: The acini were small, and only a few of them contained colloid. For the most part the lumens were filled with desquamated epithelium. Numerous Hürthle cells were

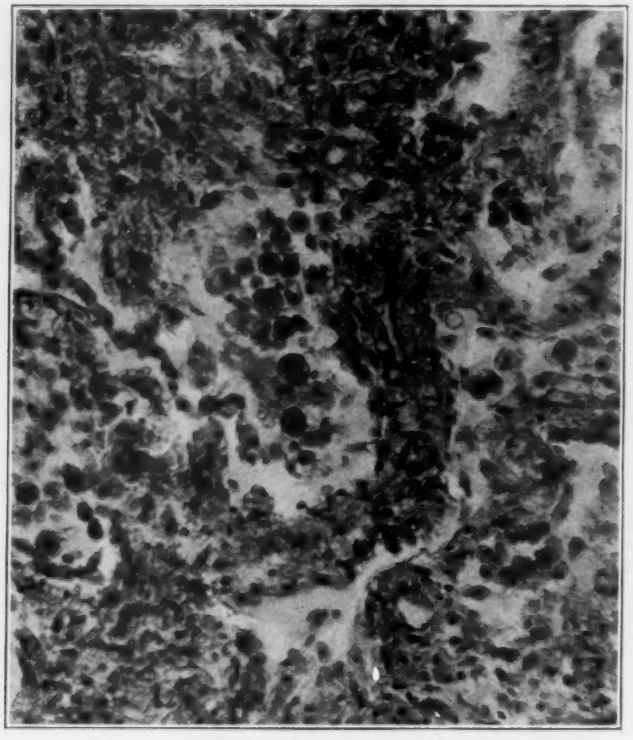

Fig. 8 (case 1).—Thickening of the alveolar septums in the lung. Hematoxylin-eosin stain; × 300.

present. There was considerable increase in the interstitial connective tissue. Throughout the sections marked lymphocytic infiltration was present, and lymphoid follicles were observed in many areas.

Aorta: There was no atheroma. The elastic tissue was normal in amount and in distribution. Slight myxomatous degeneration of the media was noted.

Voluntary Muscles: Sections from the upper intercostal muscles and the crura of the diaphragm showed conspicuous alterations. Normal muscle fasciculi alternated with fasciculi in which the individual muscle fibers were small and shrunken. In these abnormal fibers the nuclei were closer together than usual; the striations were well preserved in most instances. There was an increase in the connective tissue among the fibers, although the connective tissue between fasciculi was normal in amount. In most of the tissue inflam-

matory cellular infiltration did not accompany these changes. However, there were scattered lymphocytes and a few polymorphonuclear leukocytes in the connective tissue in other areas. Perivascular collars of lymphocytes were noted about a few small vessels. Sections of the musculature of the central portions of the diaphragm and of several other muscles did not show any deviation from normal.

Skin: The epidermis and the appendages of the skin were normal. Throughout the pars papillaris and the pars reticularis a marked increase of dense collagenous connective tissue was present. There was conspicuous fragmentation of the elastic tissue of the cutis. The subcutaneous fat was divided into lobules by rather broad and dense bands of collagenous connective tissue. The changes were those of the late stage of scleroderma.

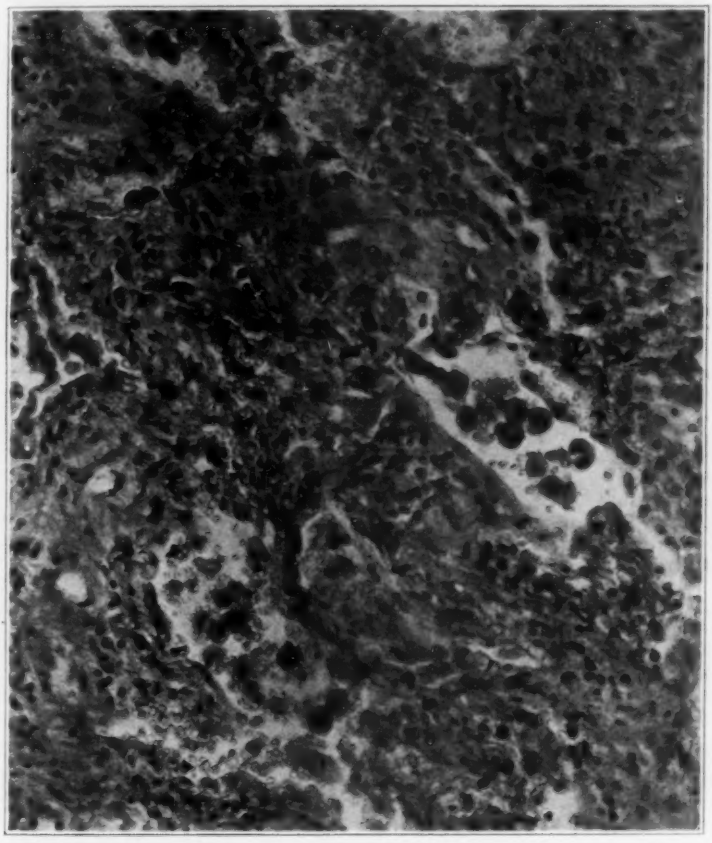

Fig. 9 (case 1).—An area of extensive fibrosis in the lung. The alveoli are widely separated from one another. They contain phagocytic cells filled with pigment. Hematoxylin-eosin stain; × 300.

Case 2.—A. N., a white widow aged 56, was admitted to Boston City Hospital in September 1937.

During the preceding year she had been weak and had lost about 20 pounds (9 Kg.) in weight. For a few months before admission she had been bothered by pains in both knees and moderate dyspnea on exertion. Later she had felt somewhat feverish in the late afternoon and had had a constant ache in the lower part of the back. This had been accompanied at times by dysuria, frequency of urination and nocturia. There was slight orthopnea at this time but no other cardiovascular symptoms. Physical examination on admission to the hospital revealed only a few rales at the bases of both lungs, a questionably enlarged heart

and slight tenderness of both knee joints. The laboratory data were not remarkable. Roentgen examination showed evidence of cardiac enlargement and early hypertrophic arthritis of the knee joints. While the patient was in the hospital her temperature remained elevated and she had mild leukocytosis. Signs of a small pleural effusion appeared on the right side, and on thoracentesis clear, yellow fluid with a specific gravity of 1.015 was obtained. This fluid contained 3,300 white cells (54 per cent polymorphonuclear leukocytes and 46 per cent lymphocytes), and the protein content was 3.3 Gm. per hundred cubic centimeters. The patient was digitalized and was discharged after six weeks' hospitalization. On discharge she still had a few rales at the base of the right lung and a slight fever.

After leaving the hospital she remained in bed most of the time, feeling weak and dyspneic. The pains in the joints remained minimal. Coldness, pain and stiffness of the hands, particularly on exposure to the cold, appeared about February 1938. In May coldness and blueness of the toes were noted, associated with pain in the shoulders and knees. There were also slight edema of the ankles and a chronic nonproductive cough at this time. During the next month occasional bouts of vomiting, orthopnea and mild shooting pains across the chest appeared, and she was readmitted to the hospital in June.

Physical examination at this time revealed a brownish tinge to the skin, particularly around the neck. Over the hands and forearms the skin was thickened and tightly bound down to the underlying structures. There were similar, but less pronounced, changes in the feet. The fingers and toes were cyanotic and cool. Examination of the retinas revealed nothing remarkable except for a small whitish area just above the optic disk on the right side. There was slight dulness at the base of the left lung posteriorly and moist rales at the bases of both lungs. The heart was enlarged to the left. There was a soft, blowing systolic murmur at the apex and a protodiastolic gallop sound. Along the left sternal border, best heard in the third interspace, there was a to-and-fro sound, interpreted as a friction rub. The rhythm was regular, and the arterial tension was 160 systolic and 110 diastolic. The edge of the liver was felt about 3 cm. below the costal margin. There was slight edema of the ankles.

Repeated urinalyses showed the specific gravity to be as high as 1.032. Most specimens of urine contained considerable albumin, a varying number of white cells and occasional hyaline and granular casts. The red cell count and hemoglobin level were normal, and the white cell count was 23,000 on admission. The results of other laboratory procedures are recorded in the table. The vital capacity was 700 cc. Roentgen examination of the chest revealed the heart to be symmetrically enlarged and the pulmonary fields clear. Later roentgenograms showed congestive changes in the lungs. Electrocardiograms showed changes indicative of partial heart block and low electromotive force. The patient continued to have mild elevation of temperature. Her symptoms persisted and she grew gradually worse and died in June, 1938.

Anatomic Diagnoses.—The anatomic diagnoses included scleroderma, myocardial fibrosis, pulmonary fibrosis, bilateral focal bronchopneumonia, chronic passive congestion of viscera, bilateral hydrothorax and multiple venous thromboses.

Autopsy.—The body was that of a well developed and well nourished woman. There was slight edema of the ankles and the face. Over the fingers the skin was stretched tightly, and the subcutaneous tissues of the region showed slight atrophy.

The peritoneal cavity contained 800 cc. of slightly cloudy, amber fluid. The peritoneal surfaces were smooth and glistening.

The right pleural cavity was largely obliterated by dense fibrous adhesions with clear, amber fluid in the spaces formed by the adhesions. There were similar fibrous adhesions over the upper lobe of the left lung. Eight hundred cubic centimeters of slightly cloudy, amber fluid was present in the lower portion of the left pleural cavity.

The pericardial cavity contained 100 cc. of slightly amber fluid. The surfaces were smooth and glistening.

The heart weighed 500 Gm. There was a moderate amount of subepicardial fat. The left ventricular myocardium measured 1.4 cm. in thickness; the right ventricular myocardium, 0.3 cm. The myocardium was soft in texture and light red in color, speckled with gray translucent areas less than 0.3 cm. in diameter. The endocardium, including the valves, was smooth. Just above the cusps of the aortic valve were several small calcified plaques. There was no narrowing of the orifices of the coronary arteries, and the lumens were normal in color, although scattered atheromatous plaques were present in their walls.

The right lung weighed 670 Gm.; the left one, 380 Gm. There were patches of bronchopneumonia throughout both lungs, most extensive in the middle and the lower lobe of the right lung. No areas of fibrosis were apparent on gross examination.

The spleen weighed 310 Gm. Externally, the organ was firm, smooth and grayish purple. The cut surface was dark purple; the pulp scraped away with difficulty.

Summary of Clinical Data

Case No.	Sex	Age at Onset of Scleroderma	Age at Onset of Cardiorespiratory Symptoms	Course of Illness	Visceral Symptoms: Raynaud's Syndrome	Arthritis	Pigmentation	Dyspnea	Orthopnea	Thoracic Pain	Cough	Edema	Gastrointestinal Symptoms	Physical Examination: Cardiac Enlargement	Murmur	Gallop	Pulmonary and Aortic Second Sounds	Usual Arterial Pressure, Systolic/Diastolic, in Mm. of Hg	Lungs	Subcutaneous Edema	Electrocardiogram	Roentgenogram	Laboratory Data: Blood Levels, per 100 Cc.	Basal Metabolic Rate, %
1	F	24	26	Died at 27	+	+	+	+	+	0	+	+	+	+	Slight apical systolic	+*	$P_2 = A_2$	140/100	Basal rales	+	Abnormal	Heart enlarged; lungs congested	Total protein. 6.7 Gm. Albumin..... 3.3 Gm. Globulin..... 3.4 Gm. Calcium..... 10.2 mg.	3+
2	F	55	54	Died at 55	+	+	+	+	+	+	+	+	+	+	Slight apical systolic	+*	?	140/ 90	Basal rales	+	Abnormal	Heart enlarged	Total protein. 5.6 Gm. Albumin..... 3.0 Gm. Globulin..... 2.6 Gm. Calcium..... 8.0 mg.	..
3	F	29	48	Living at 55	+	+	+	+	+	0	0	+	+	+	0	0	$P_2 > A_2$	165/ 85	Basal rales	+	Abnormal	Heart enlarged; mottling of pulmonary field; esophageal stricture	Total protein. 8.1 Gm.	..
4	M	46	44	Died at 46	0	+	+	+	+	0	+	+	0	+	0	+†	$P_2 > A_2$	140/ 90	Basal rales	+	Abnormal	Heart enlarged; mottling of pulmonary field	Total protein. 7.6 Gm. Albumin..... 3.0 Gm. Globulin..... 4.6 Gm. Calcium..... 10.5 mg.	+13
5	F	41	39	Living at 54	+	+	+	+	+	+	+	+	0	+	Moderately loud apical systolic	0	$P_2 > A_2$	130/ 90	Basal rales	+	Abnormal	Heart enlarged; lungs congested	Total protein. 7.3 Gm.	..
6	F	40	45	Died at 47	+	0	+	+	+	+	0	+	0	+	0	0	$P_2 > A_2$	120/ 76	Basal rales	+	Abnormal	None obtained	Total protein. 7.1 Gm. Albumin..... 4.3 Gm. Globulin..... 2.8 Gm. Calcium..... 11.3 mg.	—13
7	M	62	62	Died at 63	0	+	+	+	0	0	0	+	0	+	Slight apical systolic	0	?	110/ 70	Basal rales	+	Abnormal	None obtained	Calcium..... 8.7 mg. Cholesterol... 188 mg.	..
8	F	25	29	Died at 29	+	+	+	+	+	+	0	+	0	+	0	0	?	120/ 70	Basal rales	+	None obtained	None obtained	.....	—3
9	F	19	? 30	Living at 35	+	+	+	+	0	0	0	+	+	+	Slight apical systolic	0	$P_2 = A_2$	120/ 60	Clear	+	Abnormal	Heart enlarged; constriction of esophagus	Cholesterol... 214 mg.	—22

* Protodiastolic. † Presystolic.

The liver weighed 1,520 Gm. The external surface was dark reddish brown. Surfaces made by cutting showed prominent dark red areas at the centers of the lobules contrasting with light gray or yellow portal areas.

Fig. 10 (case 2).—A survey photomicrograph to show the extent and distribution of the myocardial lesions. Phloxine–methylene blue stain; × 11.

There was a healed stellate laceration of the cervix uteri.

A few scattered patches of atheroma were present in the aorta and slightly more extensive in the abdominal region.

The thyroid appeared normal on gross examination.

There were multiple venous thromboses. The subclavian, external jugular, internal jugular, innominate and brachial veins of the right side were filled with soft, unorganized thrombi. The right carotid sheath was thickened and adherent to the structures contained within it.

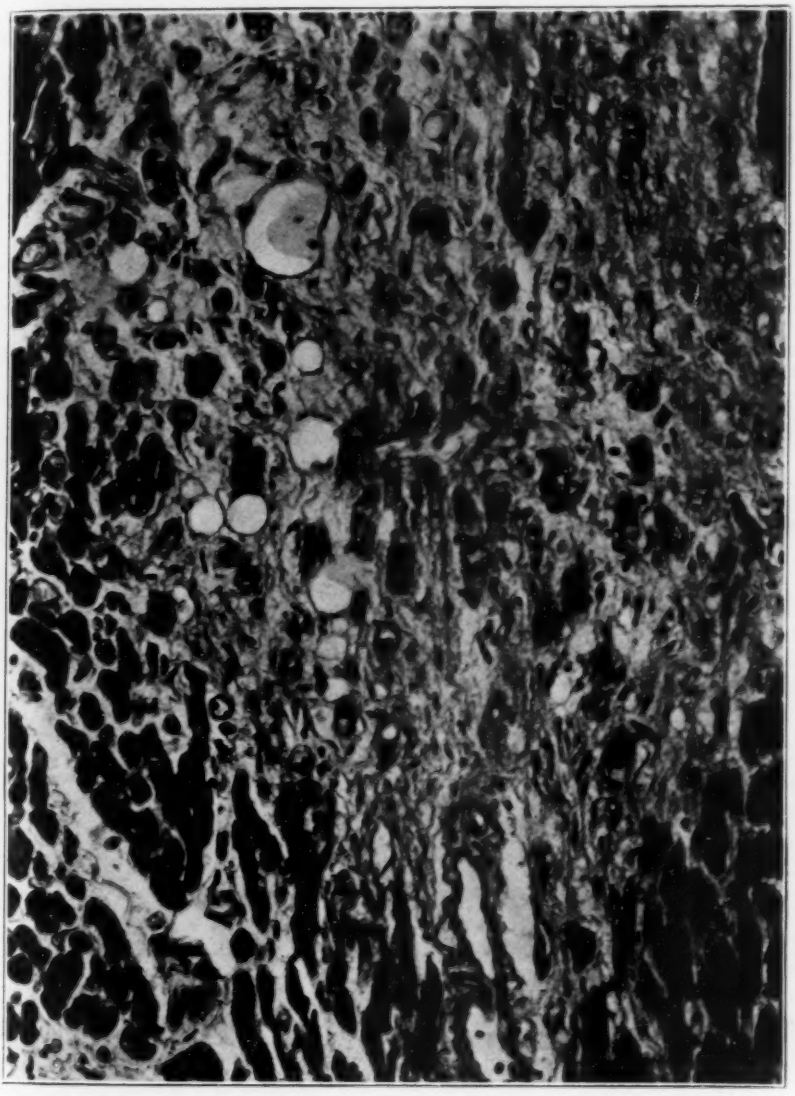

Fig. 11 (case 2).—A myocardial lesion composed of highly vascular collagenous tissue. A few fat cells and muscle fibers persist within the lesion. The resemblance to the lesions in case 1 is striking (figs. 5, 6 and 7). Phloxine-methylene blue stain; × 300.

particularly the internal jugular vein. The left subclavian vein contained a friable thrombus, as did the right greater saphenous vein. There were organized thrombi in the left femoral and external iliac veins.

The gastrointestinal tract, pancreas, gallbladder, bile ducts, kidneys, adrenals, urinary bladder, fundus uteri, ovaries, parathyroids, larynx, brain and middle ears were normal.

Microscopic Examination.—Heart: The most conspicuous lesions were irregular areas of connective tissue proliferation in the myocardium. These were distributed irregularly through the musculature, being encountered from endocardium to epicardium; they extended into papillary muscles (fig. 10). The lesions at times bore no relation to medium-sized or large arteries but at others included such vessels within the fibrous tissue. The arteries showed none or at most only slight intimal or medial thickening. None was occluded, and the lumens did not appear narrowed. The centers of the lesions were composed of collagenous connective

Fig. 12 (case 2).—The small myocardial lesion is composed of cellular collagenous tissue among somewhat atrophic muscle fibers. Phloxine-methylene blue stain; × 300.

tissue, delicate in texture. The collagen fibers were thin and somewhat separated from one another. In proportion to the number of fibers, the fibroblasts were numerous (fig. 11), but lymphocytes and mononuclear cells were encountered rarely and in only a few foci. The appearance of cellularity in the areas of fibrosis seen under low magnification was due to the number of connective tissue cells rather than to inflammatory cell infiltration. No hemosiderin deposits were observed. In all areas of connective tissue proliferation, there were many thin-walled capillaries, which were distended with blood (fig. 11).

The lesions were not sharply delimited. At their centers muscle fibers were usually absent, though occasional ones were encountered from place to place; at the periphery the connective tissue gradually became less and the muscle fibers more numerous. At times, the muscle

fibers within the areas of fibrosis were atrophic, but more often they were morphologically normal. Giant cells were not seen. The musculature between the lesions was well preserved. The lesions were of different sizes and therefore were presumed to be of different ages. The smallest lesions consisted of an increase of fibrous tissue among morphologically normal myocardial fibers (fig. 12). From the study of lesions of various sizes, it was judged that the sequence involved in the development of the lesions was a progressive increase in highly vascularized connective tissue with concomitant disappearance of myocardial fibers. There was no evidence of a primary degeneration of muscle with repair.

This interpretation of sequences was strengthened by the behavior of fat cells within certain of the lesions. Most of the areas of involvement were devoid of fat, but some of them contained a few adult fat cells, usually in groups (fig. 11). In some places in which the myocardium was less involved small groups of fat cells were found in the septums between the muscle bundles. That is, there was a mild degree of fat infiltration of the myocardium. Within some of the groups of fat cells the delicate, cellular fibrous tissue made its appearance in the same manner as in the smallest lesions among the muscle fibers. All stages could be found between such early lesions in the interfascicular fat and the large areas of fibrosis containing a few fat cells.

The fibrosis extended into the subepicardial fat in areas continuous with regions of fibrosis in the underlying muscle (fig. 13). There were no lesions confined wholly to the epicardium. The connective tissue just beneath the mesothelial surface was normal in amount. Slight intimal thickening of the coronary arteries was included in the histologic sections, but no narrowing of the lumen, atheromatous deposits or thrombi were seen.

The endocardium was normal in thickness. At several points the subepicardial connective tissue blended with that of the areas of fibrosis in the underlying myocardium.

Lungs: The pleura was moderately thickened, and its blood vessels were congested. There was acute bronchopneumonia. In addition, changes antecedent to the bronchopneumonia were present in focal areas. These regions were characterized by patches in which the alveolar walls were thickened because of an increase in coarse collagenous connective tissue. Stages could be traced from small focal thickenings of the alveolar basement membrane to connective tissue overgrowth so great as to reduce the alveolar lumens almost to obliteration. Lumens in regions of most marked fibrosis showed conspicuous cuboidal alveolar epithelium and were filled with phagocytic cells containing brown, granular pigment. The increase in connective tissue was accompanied by infiltration with numerous lymphocytes, moderate numbers of mononuclear cells and rare plasma cells. Infiltrating cells of similar character were present about the bronchi and some of the blood vessels in the relatively normal portions of the lung, as well as in the areas of fibrosis. The peribronchial and the perivascular connective tissue was increased in amount and highly vascular. Throughout the lungs, the arteries presented striking thickening of their walls, with diminution in caliber of their lumens. The increase in width of the wall was due to a concentric fibrous tissue thickening of the intima with fibrosis. This change involved arteries of all sizes, from the largest vessels to the small arterioles. There was no diminution in caliber of the veins, and their walls were well preserved with the exception of the increase in connective tissue about them, as previously described.

Spleen: There was marked chronic passive congestion. Moderate arteriolar sclerosis was present, though the walls of the larger arteries were essentially normal.

Pancreas: Moderate fatty infiltration was present, but the connective tissue was not definitely increased. The arterioles showed slight sclerosis.

Liver: There was marked chronic passive congestion; the connective tissue of the lobules and the periportal areas was normal in amount and in character.

Kidney: Some of the medium-sized arteries showed intimal thickening with atrophy of renal parenchyma and increase in connective tissue in the corresponding regions. There were no alterations in connective tissue which could not be accounted for as consequences of the vascular lesions. The arterioles were sclerosed in occasional instances. Moderate chronic passive congestion was also present.

Thyroid: The connective tissue was considerably increased rather uniformly throughout the section. Foci of lymphocytes were found in the connective tissue, but there were no germinal centers. The thyroid follicles were small and the amount of colloid reduced. There was no desquamation of the epithelium, the acini being lined by an intact, uniform layer of cuboidal cells.

Skin: Sections were taken from the abdomen and the forearm. There was a marked overgrowth of dense collagenous connective tissue of the cutis and the subcutis. This overgrowth of connective tissue extended into the subcutaneous fat along the septums between fat lobules. The elastic tissue was relatively decreased in amount, fragmented and degenerated in places. A few foci of lymphocytes and mononuclear cells were present in the lower cutis. Blood vessels were few and rather small in caliber. The epidermis was somewhat atrophic

and showed slight hyperkeratosis, though the rete pegs were preserved. The appendages of the skin were essentially normal.

The skin of the forearm was similarly altered but to a lesser degree. The changes were interpreted as those of scleroderma.

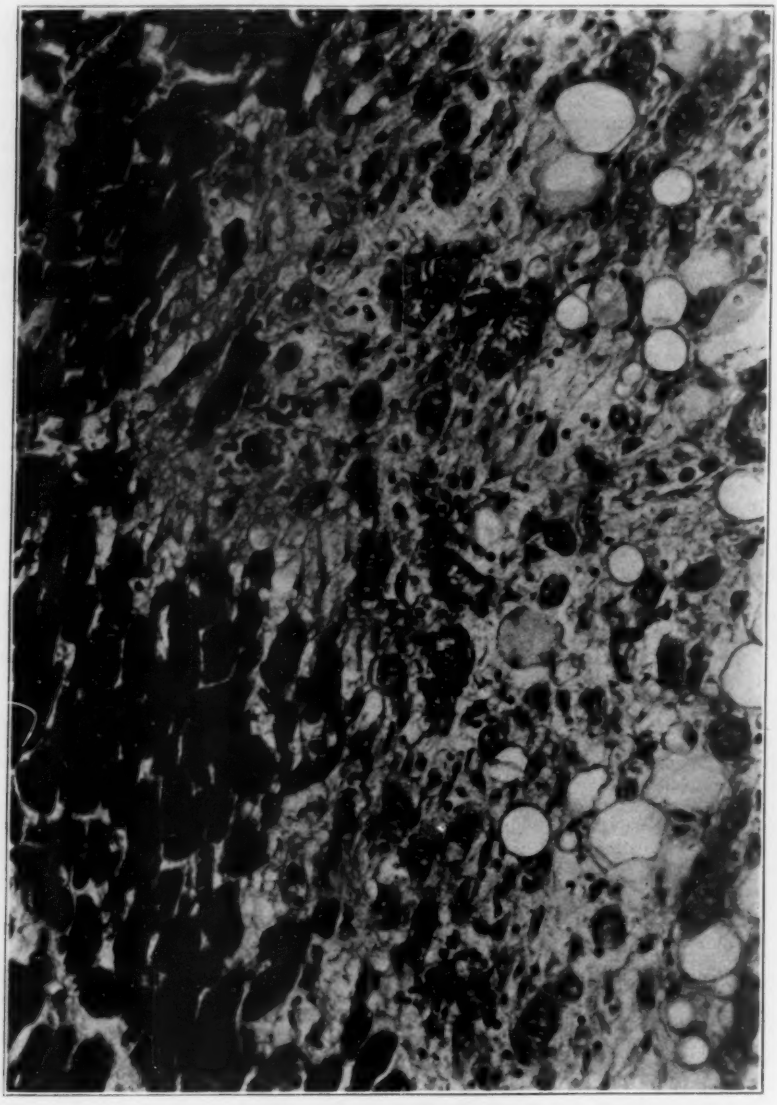

Fig. 13 (case 2).—A lesion in the superficial portion of the myocardium extending into the subepicardial fat. Phloxine-methylene blue stain; × 300.

Pituitary: There was extensive invasion of the posterior lobe of the pituitary by basophilic cells. The gland was otherwise free from change.

Miscellaneous: The adrenals, fundus uteri, ovaries, parathyroids, lymph nodes, vertebral marrow, sternal marrow, peripheral nerves and brain were essentially normal.

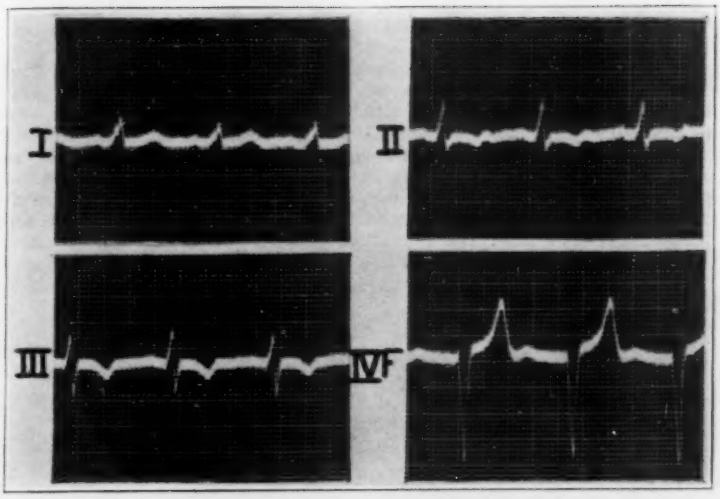

Fig. 14 (case 3).—An electrocardiogram.

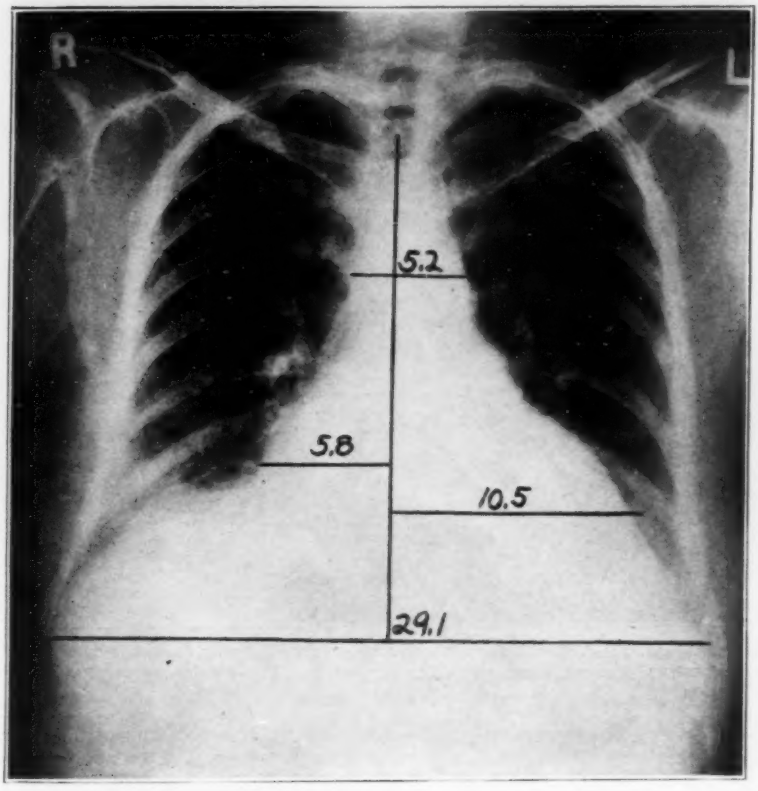

Fig. 15 (case 3).—A roentgenogram of the chest. There is marked cardiac enlargement. The bases of the lungs are mottled.

Case 3.—F. W., a Russian housewife aged 54, entered Peter Bent Brigham Hospital in 1941 because of difficulty in swallowing of several years' duration.

In 1916 she was first seen in the outpatient clinic of this hospital because of swelling of the hands associated with cyanosis and coldness of the hands and feet when exposed to cold. This process became worse, and soon the changes of scleroderma appeared in her face, arms and legs. About 1930 she began to have dyspnea on exertion and in 1934 began to have intermittent palpitation and edema of the ankles. There had been occasional bouts of marked difficulty in breathing and slight orthopnea for several years. There was no precordial pain.

Fig. 16 (case 3).—A roentgenogram of the esophagus filled with barium sulfate. There is a smooth constriction about 4 cm. above the diaphragm. The roentgenogram was reversed in reproduction.

In 1938 a new symptom appeared. She noticed difficulty in swallowing and a sensation of food sticking in her chest. There was frequent regurgitation. This became slowly worse, at times interfering with swallowing liquids. Because of this the patient was admitted to the hospital.

Physical examination on admission revealed marked sclerodermatous changes of the skin of the face, arms and legs. The hands were clawlike, and there were trophic lesions on the finger tips. The heart was markedly enlarged to the right and left. The cardiac sounds were

of fair quality, and there were no murmurs. The pulmonic second sound was accentuated. The blood pressure varied between 150 systolic and 80 diastolic and 180 systolic and 90 diastolic. The lungs were clear except for a few inspiratory rales at both bases. The laboratory data were not remarkable except for a total serum protein of 8.1 Gm. per hundred cubic centimeters. Electrocardiograms showed changes indicative of intraventricular block (fig. 14) and later of left bundle branch block.

Roentgen examination showed marked cardiac enlargement with the left border of the heart reaching the axilla (fig. 15). The heart was triangular in appearance. There was a beat of small amplitude on all borders. No auricular enlargement was seen. There was a coarse mottling at the bases of both lungs, without any other pulmonary abnormalities. Examination of the esophagus showed a smooth constriction about 4 cm. above the diaphragm and about

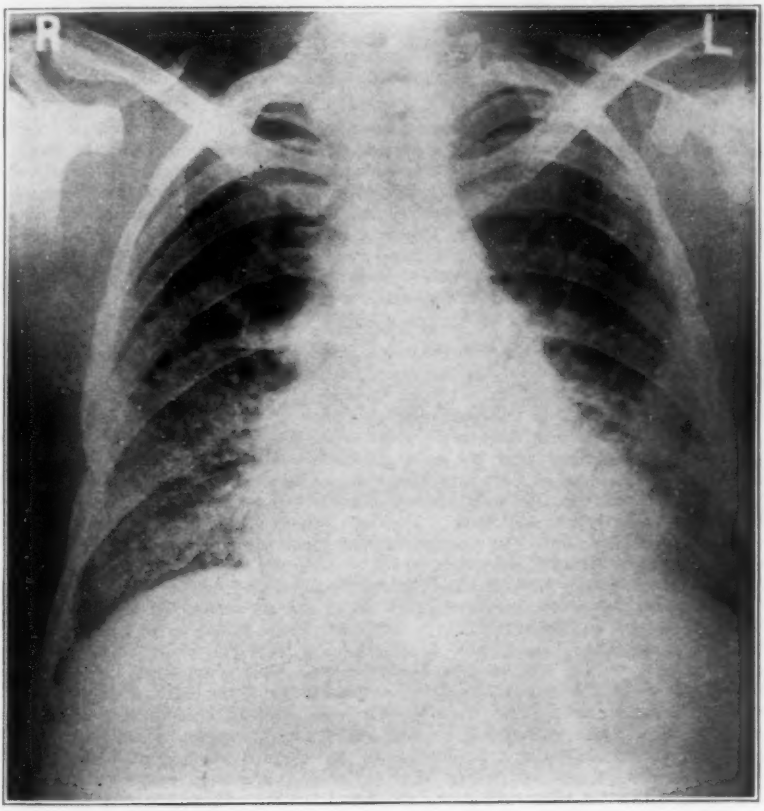

Fig. 17 (case 4).—A roentgenogram of the chest. The heart is enlarged to both right and left with hypertrophy of the right ventricle and a poor, barely visible beat. There is a diffuse mottling in the middle and the lower third of the lungs.

4 mm. in diameter (fig. 16). It did not relax after the inhalation of amyl nitrite. The stomach, duodenum and colon appeared normal on roentgen examination. Esophagoscopy confirmed the roentgen finding, and biopsy failed to reveal any abnormalities. The esophagus was dilated several times, and the patient's ability to swallow food was improved. When last seen in April 1942, she was able to eat a normal diet without any difficulty.

Case 4.—C. P., an unemployed man aged 56, was admitted to Peter Bent Brigham Hospital in 1939.

In 1915 he had worked in an "iron mine" for six months. In 1937 he was admitted to Boston City Hospital because of pains in the wrists, shoulders, hips, knees and ankles. At

that time he had a cough productive of yellowish, odorless sputum and had lost about 20 pounds in weight. Physical examination on admission revealed no abnormalities except stiff, slightly swollen and red joints. A roentgen examination of the chest showed diffuse mottling of the bases of both lungs and enlargement of the heart to the left with enlargement of the supracardiac area. Electrocardiograms showed evidence of partial heart block with a PR interval of twenty-six hundredths of a second. A diagnosis of cardiac decompensation of undetermined origin was made. Shortness of breath became the most prominent symptom, and in February 1938 he entered another hospital, where examination yielded similar results. After his discharge from that institution his symptoms continued to increase, and in August 1938 he came to the outpatient clinic of Peter Bent Brigham Hospital. Examination at this time showed smooth and thickened skin over the fingers. A roentgen examination of the chest showed the heart to be enlarged to both the right and the left with hypertrophy or dilatation of the right ventricle and a poor, barely visible beat (fig. 17). There was a diffuse mottling of both lungs, particularly the middle and the lower thirds, with the apexes fairly clear. The hilar glands appeared enlarged. Because of progressive dyspnea, cough and edema of the ankles he was admitted to the hospital in March 1939. Physical examination at that time showed sclerodermatous changes of the extremities with clubbing of the fingers. The heart was enlarged: the sounds were distant, and there were a presystolic gallop and an accentuated pulmonic second sound. There were no murmurs. The arterial pressure was 140 systolic and 90 diastolic. There were moist rales at the bases of both lungs. The liver was just palpable. There was moderate edema of the legs. The laboratory data were normal. Biopsy of the skin showed changes consistent with scleroderma. Roentgen examination of the chest did not reveal any new abnormalities. After discharge from the hospital he returned periodically to the outpatient clinic. His scleroderma became more pronounced. In October 1939 roentgen examination of the heart showed considerable enlargement with a triangular shape and prominence of the pulmonary conus. He died at home on November 30.

Case 5.—D. K., a woman aged 52, was admitted to Peter Bent Brigham Hospital in 1940. In 1927 she was seen by a physician because of weakness, dyspnea and edema of the ankles. She had vague pains in the joints at that time, and in 1929 she noted for the first time that her hands turned blue, felt cold and ached on exposure to the cold. Soon after that she began to have tightness of the skin and limitation of motion of the hands. In 1939 she suffered from a sharp stabbing pain in the upper portion of the chest, on the left side, which recurred a few months later. Soon after the pain occurred, weakness, dyspnea and edema of the ankles developed. Because of these symptoms she was admitted to Peter Bent Brigham Hospital. On physical examination on admission, she was orthopneic and the skin over the face, hands and feet was tight and inelastic. The heart was enlarged with a loud, high pitched systolic murmur at the apex. The pulmonic second sound was accentuated. The rhythm was absolutely irregular. Arterial pressure was 130 systolic and 90 diastolic. There was dulness at the bases of both lungs with diminished breath sounds and many moist rales. The liver was palpable just below the costal margin. Moderate edema of the ankles was present. Laboratory data were not remarkable. The vital capacity on admission was 800 cc., increasing to 1,250 cc. at the time of discharge. Thoracentesis yielded fluid which contained 900 white cells, 50 red cells and 4.9 Gm. of protein per hundred cubic centimeters and had a specific gravity of 1.018. An electrocardiogram showed auricular fibrillation, premature ventricular beats and left bundle branch block. Roentgen examination of the chest showed marked cardiac enlargement, both to the right and to the left, and the heart appeared triangular. There was an irregular beat of fair quality. No intracardiac calcification was seen. The lungs appeared congested, and there was fluid at both bases. The patient showed improvement during her stay in the hospital. In April 1942 she was reported to have continued evidence of myocardial failure, but no new symptoms had developed.

Case 6.—R. G., a woman aged 46, was admitted to Peter Bent Brigham Hospital in 1936. Seven years before she noted for the first time blanching of her fingers on exposure to cold, and one year later sclerodermatous changes appeared. In 1935 a cervicothoracic sympathectomy was performed, with only questionable improvement. For one year prior to admission she experienced palpitation and tired readily on exertion. She had occasional bouts of a "heavy" feeling in the precordial region. Physical examination on admission to the hospital showed sclerodermatous involvement of the arms and legs with deep pigmentation. The retinal vessels were normal. The heart was not enlarged, and the sounds were normal without murmurs. The rhythm was regular except for occasional extrasystoles. Arterial pressure was 120 systolic and 76 diastolic. Electrocardiograms showed left axis deviation and premature ventricular beats. Biopsy of the skin showed changes consistent with scleroderma.

She was discharged from the hospital and was followed up by her local physician, who stated that in April 1937 symptoms of cardiac failure developed and death occurred a few days later.

CASE 7.—L. C., a man aged 63, was admitted to Boston City Hospital in 1939 because of inability to speak and weakness of the left side of the body.

In 1937 he first began to have pains in his legs, particularly about the knee joints, and about eight months before admission he first noted cutaneous changes of a sclerodermatous nature on his legs. Although he had been slightly short of breath for years, he became much more so five weeks before entry, and one week before admission he awoke with weakness of the left side of his body and inability to speak. Physical examination showed evidences of a left hemiplegia and tight shiny skin of a sclerodermatous nature about the knees and elbows in particular, with a blotchy brown pigmentation. The heart was enlarged; the rhythm was regular, and there was a slight apical systolic murmur. The arterial pressure was 110 systolic and 70 diastolic. There were coarse rales at the bases of both lungs. An electrocardiogram showed left axis deviation. No roentgen examination of the chest was done. The patient gradually became weaker and died after one month's hospitalization. Permission for post-mortem examination was not obtained.

CASE 8.—M. F., a woman aged 28, was admitted to Peter Bent Brigham Hospital in 1936. About three years previously, six months after childbirth, she began to experience coldness and pallor of her hands on exposure to the cold. Later the hands became purple and painful under similar conditions. In 1934 her hands became swollen, the movement limited and the skin shiny. There were no cardiac or gastrointestinal symptoms. Physical examination on admission to the hospital showed sclerodermatous changes of the skin of the entire body with deep brown pigmentation. The heart was not enlarged; the cardiac sounds were normal, and the rhythm was regular. No murmurs were heard. The arterial pressure was 120 systolic and 70 diastolic. There were fine rales at the bases of both lungs, but no other pulmonary abnormalities. The laboratory data were not remarkable. About one year after discharge she was seen by her local physician because of almost constant dyspnea, edema of the ankles and occasional pains in the chest on the left side. The results of physical examination at this time were unchanged except that the heart was enlarged. She died at home in January 1937.

CASE 9.—M. L., a woman aged 25, was admitted to Peter Bent Brigham Hospital for the first time in 1932.

In 1926, soon after the birth of her first child, she noted blanching of her fingers when exposed to cold. This was often accompanied by an aching pain, and soon after this the skin gradually became tight, shiny and deeply pigmented. In 1933 roentgen examination of the chest failed to reveal any abnormalities. During the following years bilateral cervical sympathectomies and thyroidectomy were performed in an attempt to alleviate her condition. In 1937 she began to have difficulty in eating, because food seemed to catch substernally. She also began to tire more easily and gradually became somewhat dyspneic on exertion. When last seen, in March 1942, her difficulty in eating had increased slightly, but there had been no recent change in her other symptoms. Physical examination at that time showed diffuse involvement of the skin with deep pigmentation. Her heart was slightly enlarged; the cardiac sounds were of good quality, and there were no murmurs. The arterial pressure was 110 systolic and 70 diastolic. Roentgen examination of the chest revealed a marked increase in the size of the heart compared with its size at the original examination in 1933. The heart had assumed a triangular appearance, and a moderately good beat was present on all borders. There was a diffuse increase in the pulmonary markings. The esophagus showed a narrow constriction over a distance of several centimeters in the lower third of the esophagus. An electrocardiogram showed only low electromotive force. Her vital capacity was 1,200 cc., and the basal metabolic rate was —22 per cent. The cholesterol level of the blood was 214 mg. per hundred cubic centimeters. The results of other laboratory procedures were within normal limits.

The changes in the size of the heart are difficult to evaluate in this case because of the total thyroidectomy.

COMMENT

In all the cases reported here the patients showed the classic picture of scleroderma together with signs and symptoms suggesting heart failure. The data are summarized in the table. In 7 of the 9 cases the patients were women. Their ages at the onset of the cutaneous changes ranged from 19 to 62 years, the average being 38 years. In 3 cases the appearance of cardiac symptoms preceded

changes in the skin by as much as two years. Though there were symptoms of Raynaud's disease in 8 of the 9 cases, the degree of blanching and pain in the extremities on exposure to cold could not be correlated with the progression of the visceral manifestations of the disease. In all cases the patients complained of symptoms referable to the joints, usually mild, though in some cases severe pains in the joints with redness and tenderness suggested the diagnosis of rheumatoid arthritis. In all cases there was abnormal pigmentation, often associated with areas of loss of pigment. In general, both the progress of the cutaneous disease and its relation to vasomotor, joint and cardiac symptoms were extremely variable.

The evaluation of cardiac symptoms in scleroderma is difficult because the cardiac manifestations are frequently associated with pulmonary lesions and with involvement of the thoracic wall itself. In all of the cases reported here the patients complained of dyspnea on exertion; some even before the onset of the cutaneous changes, others not until the later stages of the disease. Orthopnea was definitely present in 5 cases, and there was a history suggestive of it in several others. There was paroxysmal nocturnal dyspnea in 2 cases. Cough, at times productive of whitish mucoid sputum, was a rather prominent symptom. In none of the 9 cases was there gross hemoptysis, but in 1 case not included in the present series the patient had massive hemoptysis, the cause of which was never determined. Pain in the chest occurred in 4 of the 9 cases. Its character varied considerably, but usually it was precordial rather than substernal and was not related to exertion. Edema of the ankles was present in all cases, and in some the edema was general. Early in the disease the edema may be associated with redness and heat, but in the later stages there was no clinical evidence of inflammatory reaction. In the 6 cases with a fatal termination, the symptoms of generalized congestion were present at the time of death. In all cases there was some evidence of cardiac enlargement on clinical examination. The cardiac sounds were either of normal or of less than normal intensity. The rhythm was regular in 6 cases; in 1 there was auricular fibrillation, and in 2 there were extrasystoles. In 1 case (2) a definite pericardial friction rub was heard. In 1 case there was a loud apical systolic murmur, and in 4 others a slight apical systolic murmur was audible, but in no instance was there a diastolic murmur. In 4 of the 6 cases in which it was specifically noted, the pulmonic second sound was accentuated and was louder than the aortic second sound. In 3 cases a prominent diastolic gallop sound was noted; in 2 it was protodiastolic in time, and in the third it was presystolic. The arterial blood pressure was moderately elevated in several cases. Even in the absence of cardiac failure, basal rales were often heard in the lungs. Hydrothorax and enlargement of the liver were frequent findings when the heart failed. In 1 case the spleen was slightly enlarged. Generalized lymphadenopathy was not noted in any case.

In the 6 cases in which roentgen examination of the chest was done, strikingly similar changes were encountered. In all there was cardiac enlargement, varying from a moderate to a marked degree. The heart was triangular in shape, and in most cases the beat was of poor amplitude. In 1 instance the supracardiac area appeared to be widened, and in another there was a prominent pulmonary conus. The roentgen findings did not suggest hypertensive or valvular heart disease. There was no detectable calcification in the valves. The left ventricle was not predominantly enlarged, and the left auricle was not unduly prominent. The combination of the triangular shape and the weak beat suggested to the roentgenologist the diagnosis of myxedema heart disease or of pericardial effusion. In

all of the roentgenograms there was an increase in the pulmonary markings, this usually being most marked in the lower lobes. In several cases the lungs showed a peculiar diffuse granular or mottled appearance, particularly at the bases, extending well out to the periphery but sparing the apexes. At times the changes suggested to the roentgenologist the appearance of bronchiectasis or lipoid pneumonia. In instances of heart failure hilar congestion was usually noted.

The electrocardiograms in each of the 8 cases in which they were obtained showed some abnormality. In 1 instance there was auricular fibrillation, and in 3 there were premature ventricular beats. In 3 there was abnormally low electromotive force. In 2 there was partial heart block; in another, first intraventricular block and later bundle branch block, and in a fourth instance there was left bundle branch block. In 2 instances there was left axis deviation, while in the others the electrical axis was within normal limits.

Gastrointestinal symptoms were common, appearing in 4 of the cases reported here. In case 3 there had been progressive difficulty with the passage of food through the esophagus. Roentgen examination revealed a striking constriction of the esophagus about 4 cm. above the diaphragm. The constriction did not relax after the inhalation of amyl nitrite. Esophagoscopy showed a stricture, without any evidence of mucosal abnormality. Biopsy failed to reveal any abnormality. Esophageal dilatation produced complete relief. In another case (9) the patient also had difficulty in swallowing, though it was less severe, and a roentgen examination showed a smooth constriction in the lower end of the esophagus. The patient in case 1 had symptoms of esophageal dysphagia, severe enough to suggest the diagnosis of carcinoma of the esophagus on admission to the hospital. However, roentgen examination was not done before her death. Postmortem examination failed to reveal any abnormality in the esophagus.

The case histories of 36 additional patients with scleroderma, who were studied at Massachusetts General Hospital, were reviewed. Six of these patients had symptoms referable to the upper portion of the gastrointestinal tract. Roentgen examination showed constriction of the lower part of the esophagus with dilatation above in 5 of them. In the sixth there was a diffuse dilatation of the esophagus, stomach and small intestine.

The laboratory data in the cases reported in this paper were not helpful. The red cell count, the white cell count and the hemoglobin level were essentially normal in all cases. Urinalysis revealed varying amounts of albumin in most instances, as well as red cells, white cells and granular and hyaline casts on several occasions. The total serum protein levels varied from 5.6 to 8.1 Gm. per hundred cubic centimeters in the 6 cases in which they were determined. The albumin varied from 3.0 to 4.3 Gm. and the globulin from 2.6 to 4.5 Gm. per hundred cubic centimeters. In 2 instances in which the protein content of pleural and of pericardial fluid was noted, it was unusually high for a simple transudate.[6] Blood levels of calcium and phosphorus were normal in the 5 cases in which they were determined, as was the blood level of cholesterol. In those cases in which the vital capacity was determined, it was found to be markedly diminished. The basal metabolic rate was within normal limits, except for a level of —22 per cent in 1 case (9) in which the patient had had a total thyroidectomy in an attempt to relieve her cutaneous condition.

The pathologic aspects of sclerodermatous involvement of the skin have been extensively studied, and observations on the skin in these cases serve only to con-

6. Paddock, F. K.: The Diagnostic Significance of Serous Fluids in Disease, New England J. Med. **223**:1010 (Dec. 19) 1940.

firm the descriptions in textbooks.[7] The histologic sequences of cutaneous scleroderma seem best interpreted as dependent on change in the collagenous connective tissue. The other changes in the skin may be explained as a consequence of this alteration in the connective tissue. The collagen fibers already present become thickened, and new ones are formed. In the earlier stages, illustrated in this series particularly by case 2, the cutis and the subcutis are edematous and are infiltrated with moderate numbers of lymphocytes and mononuclear cells. These cells are in part scattered through the connective tissue and in part collected about blood vessels.

As the lesion progresses, the edema and the cellular infiltration disappear and the changes in the collagenous tissue dominate the histologic picture. The individual fibers are enormously thickened and hence, besides being increased in number, occupy more space than they did originally. Secondary to this, the epidermal layer undergoes atrophy and the rete pegs become flattened. The appendages of the skin, while retained, are rendered less conspicuous because of the increase in the connective tissue among them.

The connective tissue overgrowth is confined to the collagenous type. The elastic tissue fibers, on the other hand, become fragmented and degenerate to a variable extent as they are encroached on by the collagenous fibers. Some of the larger vessels have thickened media. The small blood vessels are few and show no changes other than diminution of caliber in their capillary beds.

Since scleroderma has been especially studied by dermatologists and since material for postmortem examination is not abundant, the changes in organs other than the skin have received less attention than they merit. In this respect, knowledge of scleroderma has developed much as it has in several other diseases involving the skin, such as lupus erythematosus and sarcoid. All these diseases, however, involve the skin only as a part of the clinical and pathologic picture which includes many organs less accessible to study by inspection. Fibrosis in the lungs,[8] cardiac failure[9] and stricture of the esophagus[10] have been noted in clinical case reports of scleroderma, and pathologic studies have shown that most of the organs of the body may be involved.[4a]

The focal areas of fibrosis in the lungs in cases 1 and 2 reported here may be related to the sclerodermatous process. It is difficult to rule out foci of chronic bronchopneumonia with organization, especially in view of the extensive lymphocytic infiltration and the peribronchial fibrosis in regions of normal alveoli. However, the distribution, corroborated by the results of roentgen examinations, would be unusual in chronic bronchopneumonia. The striking vascular lesions in the lungs in case 2 were not present in case 1. They have been observed in many patients without scleroderma. For this reason, they have not been regarded as a part of scleroderma per se.

Areas of atrophy and cellular infiltration were encountered in the upper intercostal muscles and the diaphragm in case 1. These are interesting in view of the possible resemblances of scleroderma to dermatomyositis. Clearcut scleroderma and clearcut dermatomyositis are distinctly different, but there are some patients who present both clinical and pathologic changes which partake of the nature

7. McCarthy, L.: Histopathology of Skin Diseases, St. Louis, C. V. Mosby Company, 1931.

8. Murphy, J. R.; Krainin, P., and Gerson, M. J.: Scleroderma with Pulmonary Fibrosis, J. A. M. A. **116**:499 (Feb. 8) 1941. Linenthal and Talkov.[4b]

9. Gitlow, S., and Steiner, S.: Scleroderma with Special Reference to the Blood Chemistry, Arch. Dermat. & Syph. **9**:549 (May) 1924.

10. Rake, G.: On the Pathology and Pathogenesis of Scleroderma, Bull. Johns Hopkins Hosp. **48**:212, 1931. Ochsner and DeBakey.[4c] Brock.[5a]

of both disorders.[11] Here in a patient with typical scleroderma a few lesions were encountered which were suggestive but not characteristic of dermatomyositis.

The changes in the liver and the spleen were those of long-standing chronic passive congestion.

There were extensive alterations in the thyroid in case 1 and less striking ones in case 2. These consisted of atrophy of acinar epithelium with desquamation and colloid depletion together with increase in fibrous tissue. These lesions were diffuse, not focal. They are not a specific part of scleroderma but are encountered in diseases of many types. No such changes were found in the thyroid in case 9, in which the gland had been removed surgically while the patient was still in good condition. Although atrophy of the thyroid with colloid depletion and epithelial desquamation is more frequently encountered in children, it occurs occasionally in adults. These lesions have been considered in relation to lipoid nephrosis by Wolbach and Blackfan.[12]

Our attention in this study has been focused especially on the changes in the heart and the physiologic alterations resulting from them. The lesions in the heart consist of scars of unusual type. These involve the myocardium, extending to the epicardium and endocardium only secondarily and then to a slight degree. There are certain resemblances between these lesions and those due to vascular changes. There are a number of ways, however, in which the lesions encountered post mortem in the hearts of the 2 patients with scleroderma differ from those caused by vascular disease. The lesions in the myocardium in the patients with scleroderma were not in any particular relation to arteries, these structures being indifferently included in the scars or not. Furthermore, the vessels were normal or showed minor intimal thickening without thrombosis or significant diminution in the caliber of the lumen. The hemosiderin deposits often seen in areas of myocardial scarring due to vascular lesions were entirely absent. Within the scars in the hearts of the 2 patients studied post mortem the myocardial fibers were preserved in small numbers even in the centers of the lesions (fig. 6). This was true also of fat cells (figs. 7 and 11) and of blood vessels. The sequences were interpreted as a primary overgrowth of fibrous tissue with secondary destruction of other myocardial structures. The histologic nature of the lesions is different from that of the lesions of Fiedler's myocarditis, though their distribution is similar.

The connective tissue itself was rather unusual in character. Fibroblasts were numerous, imparting a cellular appearance to the lesions when they were studied with low power. The collagenous fibers were rather refractile but not coarse and increased in caliber, as are those of the skin in characteristic sclerodermatous lesions. Within the connective tissue infiltrating the myocardium, there were large numbers of capillaries distended with red cells. The lesions, then, may be characterized as focal overgrowths of cellular, vascular connective tissue with secondary degeneration of normal myocardial structures in the regions involved.

Are these myocardial lesions specifically related to scleroderma, or are they coincidental? In other words, are we dealing with scleroderma heart disease or with heart disease in patients who also had scleroderma? We feel that the evidence points toward the interpretation that the myocardial lesions are an integral

11. Banks, B. M.: Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sacks Syndrome and Polyarteritis Nodosa? New England J. Med. **225**:433 (Sept. 18) 1941.

12. Wolbach, S. B., and Blackfan, K. D.: Clinical and Pathological Studies on So-Called Tubular Nephritis (Nephrosis), Am. J. M. Sc. **180**:453 (Oct.) 1930.

part of scleroderma. The sequence involved in the development of the myocardial lesions were those of overgrowth of connective tissue, as in the skin, but the character of the connective tissue in the skin and myocardium in scleroderma was different. However, the changes in the 2 patients with scleroderma studied at postmortem examination were similar and differed in several significant respects from other varieties of myocardial scars. The pathologic observations together with the clinical data in the cases of the series indicated that scleroderma heart disease is a clinical and pathologic entity.

SUMMARY AND CONCLUSIONS

The clinical histories of 9 patients with generalized scleroderma are reported. Postmortem examinations were performed on 2 patients. These 9 patients were selected for study because they all had symptoms and signs of heart disease. Both the clinical and the pathologic studies indicate that the sclerodermatous process is not confined to the skin but involves other organs. The cardiac failure is caused by myocardial scarring of an unusual type. Roentgen examinations may show involvement of the lungs. Dysphagia is common, and esophageal stricture occurs.

These patients demonstrate that scleroderma heart disease is a clinical and pathologic entity.

Dr. N. W. Faxon, of Massachusettes General Hospital, and Drs. J. W. Manary and F. Parker Jr., of Boston City Hospital, cooperated in making several of these cases available for study.

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LEUKEMIA

A CLINICAL AND PATHOLOGIC STUDY OF ONE HUNDRED AND TWENTY-THREE FATAL CASES IN A SERIES OF 14,400 NECROPSIES

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Although a voluminous literature exists on the subject of leukemia, there have been few studies dealing with a large series of cases in which autopsy was done. For this reason we have felt justified in reporting our study to correlate clinical and pathologic observations in all types of leukemia. Most studies usually deal with only one type or with one or a few of the problems of the complex subject of blood dyscrasias. This is well illustrated in the excellent monograph by Forkner [1] on leukemia written in 1938 and by subsequent papers on this subject. In this paper we have reviewed and critically examined 123 fatal cases of leukemia. This group was selected from 14,400 consecutive autopsies performed at the Cook County Hospital from 1929 to March 1941 and represents an incidence of 0.86 per cent. With a few exceptions data from a complete postmortem examination and studies of the peripheral blood and the bone marrow were available. We believe that such a large material and its critical review justifies this publication; the largest number of cases presented in one paper until now was 77 (Ikeda [2]) encountered in 12,396 autopsies.

CLASSIFICATION

There is considerable confusion in the literature as to terminology and classification of different types of leukemia. We cannot discuss in detail the controversies regarding various types but intend to state briefly our stand on these questions. For a long time two main types have been generally recognized: myelogenous leukemia and lymphatic leukemia. Since the work of Reschad and Schilling-Torgau [3] and Sabin and associates [4] monocytic leukemia has been proved to be a definite separate entity. The so-called "Naegeli type" of monocytic leukemia and the monocytic phase of myelogenous leukemia (Downey [5] and co-workers) apparently represent only myelogenous leukemia with a marked monocytic reaction.

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1. Forkner, C. E.: Leukemia and Allied Disorders, New York, The Macmillan Company, 1938.

2. Ikeda, K.: Gastric Manifestations of Lymphatic Leukemia, Am. J. Clin. Path. **1**: 167, 1931.

3. Reschad, H., and Schilling-Torgau, V.: Ueber eine neue Leukämie durch echte Uebergangsformen (Splenozytenleukämie) und ihre Bedeutung für die Selbständigkeit dieser Zellen, München. med. Wchnschr. **60**:1981, 1913.

4. (*a*) Doan, C. A., and Wiseman, B. K.: The Monocyte, Monocytosis and Monocytic Leukosis, Ann. Int. Med. **8**:383, 1934. (*b*) Sabin, F. R.; Doan, C. A., and Cunningham, R. S.: Discrimination of Two Types of Phagocytic Cells in the Connective Tissue by the Supravital Technique, Contrib. Embryol. **16**:125, 1925.

5. Downey, H.: Present-Day Knowledge of Blood Cell Formation and Pathology, J. Iowa M. Soc. **22**:477, 1932.

Also, with Doan and Wiseman,[4a] we recognize the existence of a common ancestor of the myeloid elements, the hemocytoblast, or stem cell, and list, therefore, a fourth type, stem cell leukemia, which is represented in our series by an unusually large number of cases (28, or 22.7 per cent).

Separation of acute from chronic leukemia is difficult in certain borderline cases. However, the acute form presents a fairly characteristic complex group of symptoms, as will be discussed later. The chronic form includes illness in which there is a history of one year's duration from the onset of symptoms; accordingly, we have classified our cases under the terms acute and chronic. In a few cases grouped under chronic leukemia there was an acute exacerbation.

The term aleukemic or subleukemic leukemia, generally used for particular subtypes, seems to be a contradiction in itself. We suggest, therefore, the terms aleukemic myelosis for the myeloid form and aleukemic lymphadenosis for the lymphatic form. These blood dyscrasias manifest themselves mainly in the myeloid

TABLE 1.—*Distribution and Classification of One Hundred and Twenty-Three Cases of Fatal Leukemia According to Type of Leukemia and Sex and Race of Patient*

Type of Leukemia	Sex		Race		Total	
	Male	Female	White	Colored		
Stem cell	..	..	..	..	28	(22.7%)
Acute	11	12	15	8	23	
Acute aleukemic	1	2	2	1	3	
Chronic aleukemic	2	..	2	..	2	
Myelogenous	..	..	..	..	53	(43.1%)
Acute	19	9	21	7	28	
Acute aleukemic	3	2	4	1	5	
Chronic	15	5	16	4	20	
Lymphatic	..	..	..	..	37	(30.8%)
Acute	10	1	10	1	11	
Chronic	19	4	20	3	23	
Chronic aleukemic	3	..	3	..	3	
Monocytic	..	..	..	..	5	(4.1%)
Acute	3	2	3	1		
				1 (Chinese)	5	
Total	86	37	96	27	123	
	69.9%	30.1%	78.1%	21.9%		

or the lymphatic organs and not in the peripheral blood, and to use any word containing "-emia" seems to be illogical.

For the final classification of a case under a given type of leukemia we used all available clinical data, the peripheral blood picture, results of bone marrow studies and, as the most important aid, the necropsy report. Any case in which autopsy is not done cannot be considered as completely worked up and can be subject to criticism as to its final interpretation and classification.

INCIDENCE

Table 1 shows the distribution of our 123 cases according to type of leukemia, sex and race. One striking figure is the high incidence of stem cell leukemia, namely, 28 cases, or 22.7 per cent. In 26 of these 28 cases, or 92 per cent, the course was fulminant and illness ended fatally within a short time. This is in accordance with the general observation that the younger the patient and the more immature the type cell, the more acute the course. In only 1 case was illness really chronic, lasting six and a half years. In a second case the patient died twelve months after the onset of symptoms. In both cases of chronic illness it was of the aleukemic variety. The ratio between myelogenous, lymphatic and monocytic types is not unusual. We had

53 cases (43.1 per cent) of the myelogenous type, 37 cases (30.8 per cent) of the lymphatic type and 5 cases (4.1 per cent) of the monocytic type. Ikeda [2] reported 51 cases of myelogenous leukemia and 26 cases of lymphatic leukemia. Our percentage of cases of acute lymphatic leukemia is also higher than the figures indicated in the literature. Of the 123 cases (61 per cent), 75 represented acute leukemia, and of this number, there were 26 cases (36 per cent) of stem cell leukemia, 33 cases (44 per cent) of myelogenous leukemia and 11 cases (14.7 per cent) of lymphatic leukemia. In the remaining 5 cases (6.7 per cent) the leukemia was monocytic.

Powell [6] expressed the belief that the higher incidence of acute leukemias reported in recent publications is due to an improvement in diagnosis, especially to recognition of the leukopenic forms of the disease.

That leukemia occurs more frequently in men is generally accepted (Forkner,[1] Powell [6] and others). Our percentage of 69.9 against 30.1, a ratio of 2 males to 1 female, is a further proof. Powell reported the same ratio. In the various types of leukemia this ratio changes. Thus, in our cases we found that for myeloid

TABLE 2.—*Age Incidence of Various Types of Leukemia in One Hundred and Twenty-Three Fatal Cases*

Type of Leukemia	Age, Years								Total
	0-10	11-20	21-30	31-40	41-50	51-60	61-70	Over 70	
Stem cell									
Acute	6	3	6	3	1	4	..	..	23
Acute aleukemic	1	1	1	..	..	..	..	..	3
Chronic aleukemic	..	..	..	..	2	..	..	..	2
Myelogenous									
Acute	2	3	3	3	3	6	6	2	28
Acute aleukemic	..	..	..	1	1	1	2	..	5
Chronic	..	..	2	6	2	9	1	..	20
Lymphatic									
Acute	1	2	..	1	3	..	3	1	11
Chronic	..	..	..	..	3	10	7	3	23
Chronic aleukemic	1	..	..	..	..	2	..	..	3
Monocytic									
Acute	..	..	1	1	2	1	..	..	5
Total	11	9	13	15	17	33	19	6	123

leukemia the ratio was 37 to 16, for lymphatic leukemia 32 to 5 and for stem cell leukemia 24 to 4. Whether the ratios are only incidental or are typical is difficult to decide, as the number of reported cases in the literature is not sufficiently large.

A definitely higher incidence among white persons has been observed, and the ratio in our cases was 3 white persons to 1 colored person, or 79 per cent against 28 per cent. We had only 1 Chinese, but the percentage of Chinese patients admitted to the hospital is low.

AGE

Table 2 furnishes interesting information regarding the average age of patients with the various forms of leukemia. There was a high percentage of persons with acute leukemia (myelogenous, lymphatic and monocytic) in the older age group; namely, in 22 (29.3 per cent) of the 75 cases of acute leukemia the patients were in the fourth to the sixth decade, in 14 cases (17.3 per cent) the patients were between 61 and 80 years of age and in only 30 cases (40 per cent) were the patients in the first three decades. Only stem cell leukemia showed a marked prevalence in the first to the third decade, namely, 69 per cent, and in 7 cases (26.9 per cent) of this type the patients were younger than 10 years. In 24.2 per cent of cases

6. Powell, W. N.: Acute Leukemias, Texas State J. Med. **36**:486, 1940.

of myelogenous leukemia the patients were younger than 30 years, while in 21 per cent they were between 31 and 60 years of age and in 30.3 per cent (10 cases) they were between 61 and 80 years of age. The figures for lymphatic leukemia are similar. In 3 cases (27.3 per cent) the patients were in the first three decades, and in 4 cases (36.4 per cent) they were older than 60 years. These figures are important for diagnostic consideration, as they prove that acute leukemia is not all too uncommon in elderly patients. Therefore, if an older patient presents an indefinite clinical picture resembling that of acute leukemia, such as ulcerative lesions in the oral cavity and petechial or gross hemorrhages, the diagnosis of leukemia should be considered and excluded, even if the white cell count is low. Differential blood counts and aspirations of bone marrow should be made to rule out this possibility.

The chronic leukemias show a definite prevalence in the middle-aged group. In 34 of 48 cases (70 per cent) the patients were in the fourth to the sixth decade and in 11 cases (22.9 per cent) they were older than 60 years. In only 3 cases (6.3 per cent) were the patients younger than 30 years, and in 1 case of aleukemic lymphatic leukemia the patient was 7 years of age. In 85 per cent of the cases of myelogenous leukemia the patients were between 31 and 60 years of age, while 57 per cent of the cases of lymphatic leukemia represented the same age group.

Summarizing, we find that according to our series, leukemia does not show a definite tendency to occur in young persons, since in the same percentage of cases leukemia occurred in the first three decades and in the fourth and sixth decades. An exception was noted in the case of stem cell leukemia, which occurred chiefly in persons younger than 30 years (93.7 per cent).

SYMPTOMATOLOGY

All forms of leukemia present a multitude of symptoms and physical signs and vary so considerably that a physician needs all available laboratory methods to establish firmly a correct diagnosis. It is of more than academic and pathologic interest not only to make a diagnosis of "leukemia" but to determine the type of leukemia. Although a cure for this disease is still not known, the treatment of acute stem cell leukemia is different from that of chronic aleukemic lymphadenosis. There are no pathognomonic symptoms in leukemia, but several symptoms were encountered more frequently in some types than in others. The acute leukemias particularly show certain typical features that are not so frequently seen in the chronic form. We agree with Kaufmann and Loewenstein [7] that it is impossible to correlate clinical observations with a particular cell type.

In our series of cases we have tried to evaluate the clinical features and the results of physical examination and laboratory tests. In several cases it was impossible to obtain a complete history, since many of the patients admitted to the Cook County Hospital are foreign born and frequently were unable to speak and understand English. Many patients had not had previous medical attention and were moribund when admitted, and from them also it was impossible to obtain detailed histories.

The onset in all cases of acute leukemia was abrupt; in cases of chronic leukemia it was insidious. In 3 cases myelogenous leukemia started as chronic leukemia and then suddenly showed the symptoms of the acute form; death occurred after a few weeks. In 12 cases (acute leukemia, 8; chronic leukemia, 4) the disease was first noticed after some trivial minor surgical procedure, such as extraction of a tooth or tonsillectomy. An acute infection of the upper respiratory tract was fre-

7. Kaufmann, J., and Loewenstein, L.: A Study of Acute Leukoses, Ann. Int. Med. **12**:903, 1940.

quently the initial symptom. General weakness, malaise, easy fatigue and anorexia were mentioned in early stages of acute and of chronic leukemia—in 57.1 per cent of cases of stem cell leukemia, in 15.1 per cent of cases of myelogenous leukemia and in 29.7 per cent of cases of lymphatic leukemia. Acute inflammatory and ulcerative processes in the oral cavity or in the throat were encountered in 20 cases of acute leukemia, mostly of the stem cell and the myelogenous type, and in 7 cases of chronic leukemia. Forkner pointed out that in acute monocytic leukemia these lesions are more severe and consist of deep ulcerations with swelling of the gums and the oral mucosa, while in myelogenous and in lymphatic leukemia the lesions are milder and present only slight inflammation and petechial hemorrhages. Severe bleeding from the nose was also an initial symptom frequently observed, sometimes in association with the lesions in the oral cavity but sometimes as an isolated complaint that induced a patient to seek medical advice. This was noted in 12 cases of stem cell leukemia, in 11 cases of myelogenous leukemia, in 6 cases of lymphatic leukemia and in 1 case of monocytic leukemia.

Spontaneous hemorrhage and hemorrhagic diathesis belong to the syndrome chiefly observed in acute leukemia. Petechial hemorrhages in the skin were encountered only in 1 case of chronic aleukemic lymphadenosis and in 1 case of chronic myelogenous leukemia, while they were noted in 4 cases of acute stem cell leukemia, in 4 cases of acute myelogenous leukemia and in 3 cases of acute lymphatic leukemia. Massive gross hemorrhage may also indicate the hemorrhagic diathesis of the leukemic patient. It was observed twenty-one times in acute myelogenous leukemia and aleukemic myelosis, twelve times in acute stem cell leukemia, seven times in acute lymphatic leukemia, four times in acute monocytic leukemia, three times in chronic myelogenous leukemia and eight times in chronic lymphatic leukemia. Hemorrhages occurred in 73.3 per cent of cases of the acute form and in only 31.2 per cent of cases of the chronic form.

The hemorrhage may manifest itself as bleeding from the nose (32 cases), bleeding of the gums (19 cases), hemoptysis (9 cases), melena (8 cases), menorrhagia (6 cases), conjunctival hemorrhage (5 cases), hematemesis (5 cases), retinal hemorrhage (2 cases) and hematuria (1 case).

This hemorrhagic diathesis is, according to most authors, caused by marked thrombopenia. We encountered a distinct decrease of the blood platelets in 31 cases. Whether vitamin K deficiency is of any etiologic importance has to be studied further. We have found no references to it in the literature.

One of the less frequent symptoms either in the early or in the late stages of the disease is dull or sharp pains. It was observed in 24 cases of acute leukemia and 3 cases of chronic leukemia without any preference for one or the other type. Other symptoms were headaches (7 cases), precordial or sternal pains (5 cases), vague abdominal pains (4 cases), pains in the arms or legs (8 cases) and pains in the gums or cheeks (3 cases). The pain is apparently caused by lesions of the central or the peripheral nervous system. These lesions may consist of hemorrhages or leukemic infiltrations. Trömner and Wohlwill [8] and Schwab and Weiss [9] made extensive studies in this regard and reported frequent involvement of the nervous system.

Difficulties in breathing were observed in 23 cases (10 cases of acute leukemia and 13 cases of chronic leukemia). These symptoms, however, are too vague and too frequently observed in association with other conditions often encountered in

8. Trömner, E., and Wohlwill, F.: Ueber Erkrankungen des Nervensystems, insbesondere der Hirnnerven bei Leukämie, Deutsche Ztschr. f. Nervenh. **100**:233, 1927; Periphere Nervenerkrankung bei Leukämie, Zentralbl. f. inn. Med. **48**:996, 1927.

9. Schwab, R. S., and Weiss, S.: Neurologic Aspects of Leukemia, Am. J. M. Sc. **189**:766, 1935.

leukemic patients, i. e., bronchopneumonia, pulmonary tuberculosis and cardiac decompensation, to be of any diagnostic value.

The main and most constant abnormality revealed on physical examination was enlargement of the liver, the spleen and the lymph nodes. Table 3 gives a summary of the weights of the liver and the spleen in our cases. The lymph nodes most frequently enlarged were the cervical group. Enlargement of the lymph nodes was the outstanding feature in lymphatic and in stem cell leukemia, while enlargement of the liver and the spleen was more common in the myelogenous type. However, to a lesser degree and less frequently the lymph nodes are enlarged in myelogenous leukemia, and still less frequently enlargement of the spleen and the liver is observed in lymphatic leukemia.

LABORATORY DATA

The diagnosis of leukemia, as a rule, is definitely established by a blood and a bone marrow smear. As we did not determine the bone marrow picture for all

TABLE 3.—*Weight of the Liver and the Spleen in One Hundred and Twenty-One Cases of Fatal Leukemia* *

	Liver, Gm.				Spleen, Gm.			
Type of Leukemia	Average Weight	Under 1,500	1,500-2,500	Over 2,500	Average Weight	Under 150	150-300	Over 300
Stem cell								
Acute	1,760	8	9	4	670	5	4	15
Acute aleukemic	1,830	1	1	1	510	..	1	2
Chronic aleukemic	3,145	..	1	1	990	..	..	2
Lymphatic								
Acute	2,230	2	6	4	655	..	5	7
Chronic	2,340	2	10	7	950	2	3	16
Aleukemic	2,080	1	1	1	560	..	1	2
Myelogenous								
Acute	1,950	4	18	4	540	5	4	18
Chronic	2,890	1	7	1	1,530	1	..	18
Aleukemic	1,750	..	4	1	790	..	..	5
Monocytic								
Acute	1,945	1	4	..	335	..	3	2
	No. of Cases				No. of Cases			
Total	105	20	61	24	121	13	21	87

* Note that the largest livers and spleens occurred in cases of chronic myelogenous leukemia.

patients while they were alive but did in the majority of cases at autopsy, we shall discuss later the differential counts of the peripheral blood and the bone marrow and their relation together with the other autopsy observations.

One of the most common complications of leukemia is marked anemia. It was encountered in 103 (83.7 per cent) of our 123 cases. In 63 cases (51.2 per cent) the hemoglobin concentration was under 50 per cent. Comparable figures were obtained with the count of the red blood cells. In 70 cases (56.9 per cent) the count was below 2,500,000. In most cases the anemia was of the hypochromic type. Comparing the figures for the various types of leukemia, we found a hemoglobin concentration below 70 per cent in 64 cases (85.3 per cent) of acute leukemia and in 29 cases (60.4 per cent) of chronic leukemia. It was below this percentage in 27 (96.4 per cent) of 28 cases of stem cell leukemia, 36 cases (67.9 per cent) of myelogenous leukemia, 25 cases (67.5 per cent) of lymphatic leukemia and 5 cases (100 per cent) of monocytic leukemia.

It is a well known fact that in leukemia the total white cell count is not always markedly elevated. This holds true especially for aleukemic or subleukemic groups, but it is not infrequently observed that the white cell count is considerably below the normal range, especially in the initial or terminal stages of the disease. In some

cases the number of the leukocytes was 850 per cubic millimeter. It appears from the literature that acute leukemia may start with a granulopenic blood picture, and it is due to this fact that many instances of acute leukemia have been mistaken for agranulocytosis; even the clinical picture of the latter disease is somewhat similar to that of leukemia. It is, therefore, imperative that blood counts are performed at frequent intervals. In 6 cases (21.4 per cent) of stem cell leukemia the white cell count was below 4,000. Similar low white cell counts occurred in 5 cases of myelogenous leukemia, 6 cases of lymphatic leukemia and 1 case of acute monocytic leukemia. Relatively frequent, however, was an excessively high white cell count. In 32 cases the count was over 200,000 per cubic millimeter; 14 were cases of chronic myelogenous leukemia and 6 cases of acute stem cell leukemia. When comparing counts made at frequent intervals one observes a constant fluctuation, particularly under the influence of treatment and especially after roentgen irradiation of the spleen or bones.

As has been mentioned, the hemorrhagic diathesis in leukemia is caused in many cases by marked thrombopenia. Since platelet counts were not made in all cases, our figures cannot give the true picture in this regard. It is, however, significant that in 31 cases (41.4 per cent) of acute leukemia and in 7 cases (14.6 per cent) of chronic leukemia a marked decline (mostly below 30,000) of the thrombocytes was encountered, while in 73.3 per cent of cases of acute leukemia and in 31 per cent of cases of chronic leukemia spontaneous hemorrhages occurred. One may therefore assume that the actual percentage of cases in which thrombopenia occurs is considerably higher. Like the erythrocytes and the leukocytes, the blood platelets vary in number, as indicated in repeated counts. Minot and Buckman[10] stated that according to their series of 50 cases the number of thrombocytes may be normal, increased or decreased.

In the few instances in which studies of the bleeding and clotting time were made the bleeding time was prolonged in 4 cases of acute stem cell leukemia, in 1 case of acute myelogenous leukemia and in 3 cases of acute aleukemic myelosis, while it was normal in 3 cases of acute stem cell leukemia and in 1 case of acute aleukemic myelosis. The clotting time was prolonged in 2 cases of acute stem cell leukemia and in 1 case of acute lymphatic leukemia and was within normal range in 1 case of acute stem cell leukemia, in 1 case of acute myelogenous leukemia and in 3 cases of acute aleukemic myelosis. Forkner mentioned only briefly that the coagulation time in cases of acute leukemia may be prolonged.

Considerable work has been done on the influence of leukemia on the basal metabolic rate. As early as 1869 Voit and Pettenkofer observed a marked elevation of the basal metabolic rate in a case of leukemia. Later their observation was confirmed by many authors (Minot and Means,[11] Gunderson,[12] Riddle and Sturgis[13] and others). Krantz and Riddle[14] and Lennox and Means[15] have expressed the

10. Minot, G. R., and Buckman, T. E.: The Blood Platelets in Leukemias, Am. J. M. Sc. **169**:477, 1925.

11. Minot, G. R., and Means, J. H.: Metabolism—Pulse Ratio in Exophthalmic Goiter and in Leukemia with Remarks to Similarities in the Symptomatology of These Diseases, Arch. Int. Med. **33**:576 (May) 1924.

12. Gunderson, A. H.: The Basal Metabolism in Myelogenous Leukemia and Its Relation to the Blood Findings, Boston M. & S. J. **185**:785, 1921.

13. Riddle, M. C., and Sturgis, C. C.: Basal Metabolism in Chronic Myelogenous Leukemia, Arch. Int. Med. **39**:255 (Feb.) 1927.

14. Krantz, C. Q., and Riddle, M. C.: The Basal Metabolism in Chronic Lymphatic Leukemia, Am. J. M. Sc. **175**:229, 1928.

15. Lennox, W. G., and Means, J. H.: Study of Basal and Nitrogenous Metabolism in a Case of Acute Leukemia During Roentgen-Ray Treatment, Arch. Int. Med. **32**:705 (Nov.) 1923.

belief that the basal metabolic rate is of prognostic value and an indicator of the severity of the leukemic process. A sudden sharp rise in the basal metabolic rate is a sign of bad prognosis. There are cases in which the basal metabolic rate is 100 per cent above normal. To what extent this increase is actually caused by the leukemic process is difficult to evaluate, since accompanying hyperthyroidism is observed in cases of leukemia. Of 11 cases in which the basal metabolic rate was determined, there was an elevation over 10 per cent in 10 and in 1 it was within normal limits.

Of some value is determination of the urea nitrogen and the nonprotein nitrogen in the blood of leukemic patients. Becher and Herrmann [16] reported that these substances were elevated. Of the 20 cases in which determinations were made, the level of nonprotein nitrogen was normal in 9 and considerably elevated in 11.

The uric acid content of the blood was increased in 5 cases.

The cholesterol content of the blood was normal in 3 cases and was increased in 1 case. Mueller [17] reported subnormal values in 3 cases of lymphatic leukemia and 13 cases of myelogenous leukemia.

Before concluding the discussion of the symptomatology of leukemia a few symptoms which were less frequently observed and which are referable to the leukemic process are worth mentioning. Occasionally, patients complain of edema of the extremities, which could be verified on physical examination. Those cases in which the edema is caused by a cardiorenal pathologic condition should be excluded as possible instances of leukemia. Edema in cases of leukemia could be explained by encroachment of the enlarged lymph nodes on the large vessels in the groin or by obliteration of the lymphatics by the leukemic tissue within the nodes. As will be shown later, frequently the entire normal architecture of the lymph node is destroyed and replaced by pathologic cells and tissue. No lymph sinuses were recognizable. We encountered this symptom in 8 cases of myelogenous leukemia, in 2 cases of stem cell leukemia and in 2 cases of lymphatic leukemia.

Vertigo, observed not infrequently in leukemia, is caused by infiltration of leukemic tissue into the internal ear. Gottstein [18] and Politzer [19] reported cases in which leuekemia simulated Ménière's syndrome. We encountered the symptom of vertigo in 9 cases.

In textbooks great importance is attributed to the occurrence of priapism in leukemia. We encountered the symptom in only 1 case of acute myelogenous leukemia. Craver [20] encountered it only once in his series of more than 100 cases and Barney, Hunter and Mintz [21] once in 51 cases. Warthin,[22] however, reported the occurrence of priapism in one fourth of his cases.

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16. Becher, E., and Herrmann, E.: Das Zustandekommen der hohen Werte des gebundenen und freien Aminostickstoffes im enteiweissten Blute bei Leukämien, München. med. Wchnschr. **73**:1312, 1926.

17. Mueller, G. L.: The Cholesterol Metabolism in Health and in Anemia, Medicine **9**: 130, 1930.

18. Gottstein, J.: Ueber den Ménière'schen Symptomen-complex, Ztschr. f. Ohrenh. **9**: 37, 1880.

19. Politzer, A.: Pathologische Veränderungen im Labyrinthe bei leukämischer Taubheit, Cong. internat. d'otol., Compt. rend., Basel **3**:139, 1885; cited by Forkner.[1]

20. Craver, L. F.: Priapism in Leukemia, S. Clin. North America **13**:472, 1933.

21. Barney, J. D.; Hunter, F. T., and Mintz, E. R.: Urological Aspects of Radio-Sensitive Tumors of Blood-Forming Organs, Tr. Am. A. Genito-Urin. Surgeons **24**:413, 1931; J. A. M. A. **98**:1245 (April 9) 1932.

22. Warthin, H. S.: Death Due to Leukemic Infiltration of the Larynx, Priapism Persistent Postmortem, Myeloid Thromboses in the Corpora Cavernosa, Fatal Hemorrhage from Spleen After Prolonged Radio Therapy, Internat. Clin. **4**:280, 1909.

DIAGNOSIS

Of 112 cases of our series in which a definite clinical impression was recorded, the diagnosis of leukemia was correct in 87, or 77.7 per cent. Cases in which a clinical diagnosis of one type of leukemia was made and autopsy revealed another type were counted as instances of correct diagnosis, but when the clinical impression was "blood dyscrasia" without further specification, it was not considered a correct diagnosis.

A few wrong clinical diagnoses may be mentioned: lobar pneumonia or bronchopneumonia, 3 cases; Vincent's angina, 1 case; chronic aleukemic stem cell leukemia mistaken for Hodgkin's disease, 1 case, and rheumatic heart disease, sepsis caused by Streptococcus viridans or arteriosclerotic heart disease, 7 cases. A malignant growth in the gastrointestinal tract or a bleeding peptic ulcer was suspected in 2 cases of acute myelogenous leukemia and a mediastinal tumor in 1 case of acute stem cell leukemia. A diagnosis of splenomegaly was made in 1 case of acute aleukemic myelosis. In 2 cases chronic lymphatic leukemia was discovered incidentally at autopsy.

It is not our purpose to discuss in detail the differential diagnosis of leukemia. It may suffice to mention that the so-called "leukemoid reactions" have to be clearly differentiated from true leukemia. A blood picture simulating that of leukemia may be observed in association with pertussis, infectious mononucleosis, tuberculosis, Vincent's angina and any other infectious disease. Neoplasms, such as carcinoma and melanoma, may present a similar picture. Much more difficult at times is the demarcation of leukemia from lymphosarcoma and Hodgkin's disease.

ANATOMIC OBSERVATIONS

In reviewing the necropsy reports here we shall be particularly concerned with the organs of the hemopoietic system, i. e., the liver, the spleen and the bone marrow. In a number of our cases in which the clinical diagnosis was vague or incorrect the true condition was determined after autopsy. The pathologic changes in the spleen, the liver and the bone marrow were characteristic of leukemia.

In table 3 are given the weights of the liver and the spleen in all cases in which they were recorded. In 105 cases the weight of the liver was mentioned, while in 121 cases the weight of the spleen was noted. The liver was usually large and the highest weights were noted in the cases of chronic myelogenous leukemia. This also held true for the size of the spleen. However, the size and the weight of the liver and the spleen are not diagnostic criteria in differentiating the type of leukemia, as seen from our statistics. The largest liver in our series weighed 5,535 Gm. and occurred in a patient with chronic myelogenous leukemia. The largest spleen occurred in a patient with chronic lymphatic leukemia, and its weight was 2,865 Gm.

The microscopic appearance of the liver in all types of leukemia is characteristic. The liver may show leukemic cells either within the dilated sinusoids or within the periportal fields. In only about 50 per cent of cases the connective tissue of Glisson's capsule shows a marked infiltration with mature and immature lymphocytes or myeloid cells. According to Jaffé [23] a typical feature of monocytic leukemia is the presence within Kupffer's cells of granules which yield a positive oxidase reaction. This statement was borne out in 3 of our 5 cases of monocytic leukemia, but such granules were occasionally observed in cases of myelogenous leukemia. The type cell of myelogenous leukemia found in the liver is the myeloid cells in all stages of development. In the acute forms mainly the blast cells were

23. Jaffé, R. H.: Personal communication to the authors, 1937.

observed, which frequently gave a negative oxidase reaction. The microscopic picture of the liver in the so-called "aleukemic" forms did not differ from that in the fully developed leukemias. The spleen was similar in this respect. Occasionally, an increased amount of hemosiderin pigment was seen in the liver.

The microscopic appearance of the spleen is characteristic. In almost all cases of myelogenous leukemia the spleen shows the so-called "myeloid metaplasia." The normal architecture is completely replaced by myeloid tissue showing mainly immature myeloid cells. In the acute forms, the early cell types, that is, the myeloblasts, are predominant, and mitotic figures are prominent. The oxidase reaction in many cells is negative. In the chronic forms, the more mature cells dominate the picture, myelocytes and mature granulocytes are the most common cells and the oxidase reaction is positive. Occasionally, eosinophilic myelocytes and granulocytes are seen in increased number. Not infrequently marked hemosiderosis is noted, indicating an increased destruction of erythrocytes. Important is the fact that the structures of the spleen and the liver in aleukemic myelosis do not differ from those in leukemias in which the peripheral blood shows all immature forms.

In stem cell leukemia the type cell is displayed predominantly in the spleen, but besides this cell frequently myeloid or immature lymphoid cells can be found. As in myeloid leukemia, erythroblasts and normoblasts are among the cells constituting the myeloid metaplasia.

In all forms of lymphatic leukemia the spleen presents a monotonous and uniform picture. Again, the normal architecture is completely obliterated, and one sees a uniform mass of lymphoid cells, mostly lymphocytes and lymphoblasts. The oxidase reaction is negative. In only a few cases can marked siderosis be observed.

In the few cases of monocytic leukemia studied monocytes and monoblasts dominated the picture.

Lymph Nodes.—The lymph nodes were frequently involved. Acute stem cell leukemia produced the most marked enlargement of almost all the groups of regional lymph nodes. The mesenteric and other abdominal nodes were most frequently involved in all types of leukemia. The inguinal, cervical and axillary nodes were less frequently enlarged.

The microscopic appearance of the lymph nodes varies, naturally, in the different types of leukemia. A monotonous picture is seen in all cases of lymphatic leukemia, in which the nodes are transformed into a uniform mass of lymphocytes and lymphoblasts. There is no recognizable suggestion of any normal architecture. In myelogenous leukemia one sees "myelogenous metaplasia" similar to that observed in the spleen and the liver. All forms of mature and immature myeloid cells can be observed. Only remnants, if any, of the former structures are left. Immature red blood cells are present. In stem cell leukemia the type cell replacing the lymphoid tissue is the stem cell, which gives a negative oxidase reaction. Frequently also, immature lymphoid or myeloid cells constitute the "leukemic tissue." Monocytic cells were mostly seen in acute monocytic leukemia. In 18 cases (stem cell leukemia, 5; myelogenous leukemia, 4, and lymphatic leukemia, 9) a diffuse infiltration of the leukemic cells into the capsule of the lymph node and into the perinodular tissue was noticed. This observation may be relevant in the consideration of the nature of the leukemic process as an infiltrating growth, a feature usually considered as a criterion of a malignant tumor. This supports the theory that leukemia is a neoplastic disease. In 1 of our cases there was a definite malignant degeneration of a group of mediastinal lymph nodes into a lymphosarcoma with multiple metastases.

Bone Marrow.—Most important of all is examination of the bone marrow. It reveals best the true picture of the disease, and by comparing its cells with those of the peripheral blood one can often reconstruct and follow the course of a leukemic disorder. The reports in the literature and the experience of hematologists indicate how the blood picture may change considerably during the course of the disease. It is, therefore, of the utmost importance to follow these changes by repeatedly making blood counts, smears and sternal punctures in order to obtain the true picture.

In the following paragraphs we shall give a brief summary of the bone marrow studies as compared with the peripheral blood picture in our series of cases. Most of the bone marrow counts were made on marrow obtained from the femur at autopsy.

Acute Stem Cell Leukemia: Smears of bone marrow and of blood were studied in 23 cases. In 15 cases a differential count of the bone marrow was made. In all but 4 cases the marrow was described as hyperplastic and very cellular. In 4 cases the marrow was fatty. In 17 cases (74 per cent) the majority of cells were stem cells. In 6 cases the percentage of stem cells in the marrow corresponded roughly to that in the peripheral blood. In 11 cases the predominant cell in the marrow was the stem cell; in 7 of these 11 cases the peripheral blood showed a further maturation of the cells in the direction of the lymphoblast, while in 4 cases the type cells in the peripheral blood were myeloblasts or myelocytes.

In 4 cases the bone marrow contained only a moderate number of stem cells, while lymphoid or myeloid cells dominated the picture; the peripheral blood, however, showed a higher percentage of stem cells than the marrow, indicating a dedifferentiation of cells. In 1 case transitional forms between stem cells and myeloblasts were the outstanding cell type in the marrow, while the blood smear showed 56 to 94 per cent stem cells. These figures represent average values obtained from repeated counts. In all forms of leukemia three trends of development are recognizable: a gradually increasing output of mature cells, an increased number of immature cells in the marrow and the peripheral blood and an irregular fluctuation of the circulating cells.

The bone marrow, and to a lesser degree the peripheral blood, show a large variety of cell types in stem cell leukemia, in contrast to the number in lymphatic leukemia. All stages of erythropoiesis, myelopoiesis and lymphopoiesis can be seen, but the type cell remains the undifferentiated stem cell, or hemocytoblast. Numerous mitotic figures can be seen.

Acute and Chronic Aleukemic Stem Cell Leukemia: Five cases were studied. In only 1 case was the marrow fatty; in the other 4 cases it was hyperplastic and very cellular. In all cases the stem cells formed 40 to 80 per cent of the marrow cells; a large percentage of erythroblasts was also seen but only an occasional immature myeloid or lymphoid cell. The peripheral blood showed no appreciable abnormalities; in only 2 cases moderate relative lymphocytosis was observed.

Acute Myelogenous Leukemia: Twenty-three cases were studied; in 1 case only was the bone marrow available, while in 4 cases the bone marrow was described as fatty and containing only a small number of myelocytes or myeloblasts. The peripheral blood in these 4 cases showed a corresponding number of these cells. In the remaining cases cells in all stages of myelopoiesis could be seen; in some the blast forms were predominant, and in others the more mature forms, such as myelocytes or juvenile granulocytes, predominated. In most cases the differential count of the marrow corresponded approximately to that of the peripheral blood. The percentage of erythroblasts or megaloblasts varied from 1 to 20. However, in 1 case 95 per cent of the marrow cells were erythroblasts, while in the

peripheral blood 97 per cent of the white cells were myeloblasts, 1 per cent were neutrophilic granulocytes and 2 per cent were lymphocytes. In another case there was marked eosinophilic granulopoiesis, 60 per cent of all the marrow cells being eosinophilic myelocytes, 11.4 per cent myeloblasts and 1.6 per cent neutrophilic granulocytes. The smear of peripheral blood in this case consisted of 32 per cent eosinophilic granulocytes, 50 per cent myeloblasts, 10.5 per cent polymorphonuclear granulocytes, 2 per cent neutrophilic promyelocytes, 3.5 per cent mature eosinophilic granulocytes and 5.5 per cent lymphocytes. In most cases the bone marrow contained more blast forms than did the peripheral blood.

Acute Aleukemic Myelosis: Five cases could be studied, but in 1 case a blood smear was not available. In the other 4 cases the bone marrow was very cellular and hyperplastic and contained immature myeloid cells, mainly neutrophilic myelocytes and erythroblasts. Mature granulocytes, plasma cells and lymphocytes were only occasionally observed. The blood smear in those cases in which it was available showed marked granulopenia (6 per cent of cells) but contained 16 per cent erythroblasts, 24 per cent monocytes, 50 per cent lymphocytes and 4 per cent "irritation forms." In 2 other cases it showed up to 6 per cent myelocytes and 2 per cent myeloblasts.

Chronic Myelogenous Leukemia: In all 17 cases studied the bone marrow was hyperplastic and very cellular. The differential counts of the marrow resembled each other considerably. Cells of all stages of myelopoiesis and erythropoiesis were seen, predominantly neutrophilic myelocytes, promyelocytes and metamyelocytes. Occasionally, monocytoid cells were observed. The peripheral blood resembled the marrow in its constituents. However, in 1 case the marrow contained 17 per cent myeloblasts, 12.6 per cent promyelocytes and 1.6 per cent metamyelocytes, while the blood smear showed 24 per cent myeloblasts, 9.4 per cent promyelocytes and 27 per cent metamyelocytes. In another case 65.1 per cent myeloblasts were counted in the marrow, but the peripheral blood smear showed 8 per cent myeloblasts and at a second count 54 per cent myeloblasts and only 20 per cent myelocytes. A third case is worth mentioning, because the marrow showed nothing remarkable except 0.3 per cent myeloblasts but the blood smear showed 13.6 per cent myeloblasts.

Chronic Myelogenous Leukemia with Acute Exacerbation: The marrow in the 3 cases studied did not present any remarkable features different from the marrow in other cases of myelogenous leukemia. It is important, however, to note that in 2 cases during the chronic phase the peripheral blood contained mainly myelocytes and only 1 per cent myeloblasts, while in the terminal acute phase the percentage of myeloblasts rose to 81 and 95, respectively, the highest count for myeloblasts in our series.

Acute Lymphatic Leukemia: As do all the other organs, the bone marrow presents a monotonous picture in all forms of lymphatic leukemia. In 7 of the 11 cases in our series the bone marrow was hyperplastic and cellular. It consisted almost exclusively of lymphocytes or lymphoblasts (81 to 95 per cent) in almost all cases. The balance of the marrow cells were mature and immature myeloid cells, erythrocytes and erythroblasts. The blood smear presented a similar picture. On repeated blood counts distribution of the cells varied only slightly.

Chronic Lymphatic Leukemia: Only 15 of 23 cases could be studied completely. The bone marrow was hyperplastic in 13 cases and fatty in 4. The picture was the same as that described for acute lymphatic leukemia. The majority of the marrow cells were mature or immature lymphoid cells (80 to 95 per cent). Only in 4 cases were active myelopoiesis and erythropoiesis seen. But even in those

cases the peripheral blood showed predominantly lymphocytes and lymphoblasts. In 1 case repeated blood smears showed a gradual decrease of the granulocytes from 80 to 6 per cent, while the lymphoid cells rose in the same time from 15 to 92 per cent.

Chronic Aleukemic Lymphadenosis: In 1 case the bone marrow was fatty, and in another case it was very cellular and hyperplastic. The first case is not remarkable, as the bone marrow showed lymphocytes and lymphoblasts and only a few myeloid cells. The peripheral blood, however, had 47 per cent granulocytes and 49 per cent lymphoid cells.

Acute Monocytic Leukemia: All 5 cases were studied completely. The marrow was hyperplastic and contained 70 to 96 per cent monocytoid cells (monocytes and monoblasts). Besides these cells, however, mature and immature myeloid cells and erythroblasts could be seen in varying numbers. The lymphocytes were less prominent, not more than 7 per cent. With the exception of 1 case the percentage of the monocytes was less in the blood than in the marrow. In this case a large number of monoblasts (up to 32 per cent) were present in the peripheral circulation. One case is remarkable in that the marrow contained 96 per cent monocytoid cells and only 0.4 per cent myelocytes, while the blood smear showed 90 per cent myeloblasts. In another case, the percentage of monoblasts rose gradually from 0 to 7 to 32, while the corresponding percentages for the monocytes were 25, 68 and 25. In all but 1 case the peripheral blood contained monocytes and monoblasts; in 2 cases the immature cells outnumbered the mature monocytes.

LEUKEMIC INFILTRATIONS

Accumulation of immature white corpuscles is not limited to the hemopoietic organs. We encountered the so-called "leukemic infiltrations" in almost all organs and tissues of the body. There is apparently no particular recognizable preference of one cell type for any special organ or organ system. The most frequently involved organ in all forms of leukemia is the kidney (in 78 cases, or 63 per cent). The myeloid or lymphoid cells are found within the glomerular tufts or in the interstitial connective tissue. In 5 cases the renal capsule and the perirenal fatty tissue also showed marked infiltration with leukemic cells.

The heart was involved in 43 cases (34 per cent). Here the cells were encountered within the capillaries and in the interstitial tissue between the myocardial fibers. While the infiltration of the kidney was evenly distributed among the various forms of leukemia, we encountered the highest percentage of cardiac involvement in acute stem cell leukemia; in 14 cases (54 per cent) the heart showed marked infiltration with stem cells. The heart was involved in 54 per cent of cases of acute lymphatic leukemia. In all the other forms an infiltration of the heart was not present in more than 25 per cent of cases.

The intestines showed leukemic infiltrations in 17 cases (13 per cent). Among the other organs or structures which were less frequently infiltrated with immature white cells we mention in the order of frequency only the lungs (16 cases), adrenals (14 cases), thymus (12 cases), pancreas (9 cases), central nervous system (8 cases), skin (5 cases), oral cavity (5 cases), genitalia (5 cases), thyroid (2 cases), ribs (2 cases) and urinary bladder (1 case). The infiltrations in the skin and the central nervous system are important from the clinical standpoint as they may cause severe symptoms; in the skin they appear as diffusely distributed nodules, while in the central nervous system they may give rise to such symptoms of irritation or paralysis as headaches, convulsions, vertigo, blindness, deafness or paralysis of the extremities.

On the other hand, from the pathophysiologic standpoint it is important to note that the organism reacts even in leukemia as in an infection, with the output of mature polymorphonuclear leukocytes, although an abundant number of immature white cells are present in the blood and in the tissues. The exudate in pneumonia and the pus in phlegmons or abscesses consists chiefly of mature polymorphonuclear leukocytes. In a case of chronic lymphatic leukemia a phlegmon of the buttocks and a septic infarct in the lung consisted of normal pus cells; an abscess of the lung in a case of stem cell leukemia contained only a small number of stem cells, and in a case of chronic myelogenous leukemia the base of an extensive erosion of the cervix was diffusely infiltrated by lymphocytes.

Apparently, the immature white cells have no phagocytic power, and to combat the invading lymphocytes the organism sends out the regular troops, the pus cells, as in the case of any infectious disease.

HEMORRHAGES

Petechial or massive hemorrhages were one of the common clinical symptoms of all types of leukemia, occurring mainly, however, in the acute forms. The autopsy reports show that the hemorrhages may be more extensive and may involve more organs than physical examination can reveal. The most widespread and extensive hemorrhages were encountered in cases of acute stem cell leukemia and acute myelogenous leukemia. The most frequently involved organs were the skin, the gastrointestinal tract, the epicardium, the endocardium, the conjunctivas and the pleuras.

ASSOCIATED DISEASES

In reviewing our cases of leukemia we were interested in the associated diseases discovered incidentally at necropsy. The diseases encountered are no doubt coincidental and have no relation to leukemia.

The complication most frequently encountered (forty-four times) was bronchopneumonia and lobar pneumonia; in 14 cases of chronic lymphatic leukemia alone pneumonia was the cause of death. Remarkable was the frequent incidence of hyperthyroidism and nodular goiters in association with all forms of leukemia. We encountered it in 18 cases (14.6 per cent). We have already discussed the elevation of the basal metabolic rate and could not confirm reports found in the literature that the basal metabolic rate of patients with leukemia is generally elevated.

The finding of tuberculosis in 16 cases, or 13 per cent, is not unusual, since the general autopsy material in the Cook County Hospital shows a high incidence of tuberculosis. The occurrence of hydrothorax in 13 cases, ascites in 10 cases and hydropericardium in 8 cases is also not particularly high. These transudates apparently do not represent the expression of a separate disease but are symptoms of the leukemic process and of a disturbance of the circulation of lymph or blood. The enlarged lymph nodes often compress blood or lymph vessels, causing congestion and transudation in the dependent regions.

Ulcerative proctitis and colitis were encountered in 7 cases, all acute stem cell leukemia. Ulcerative processes in the oral cavity were not uncommon in the acute phase. Numerically much less prominent but important for the concept of the disease was the association of other malignant conditions of the hemopoietic system. We observed 1 case of multiple myeloma and 1 case of myelosarcoma in association with chronic lymphatic leukemia and with acute myelogenous leukemia, respectively.

TREATMENT

Since leukemia is a hopeless and incurable disease, we need to say only a few words about treatment. The most widely used therapeutic measure, according to the literature and in our series of cases, was repeated transfusion of blood. Transfusions were given in all stages and types of leukemia, and frequently a favorable temporary response could be noticed. The treatment of second choice is roentgen or radium irradiation of the spleen, the mediastinal region, long and short bones and enlarged lymph nodes. Total irradiation of the whole body was employed. While the transfusions never had any untoward effect, exacerbation of symptoms and a rapid downhill course of the patient were frequently observed after irradiation in cases of acute leukemia, without any reference to the type of leukemia. This is in accordance with the reports in the literature. Forkner,[1] Stengel and Pancoast [24] and Minot and Isaacs [25] expressed the opinion that roentgen ray treatments were contraindicated in case of acute leukemia. Naturally, severe anemia, leukopenia, thrombopenia and a too rapid decrease of the myeloid elements would indicate a discontinuation of irradiation in any type of leukemia. An increased output of immature cells, especially of the blast type, denotes a harmful effect of irradiation.

Arsenicals were administered in several cases but without any demonstrable value.

Transfusions of bone marrow and therapy with sulfonamide compounds have proved of no avail.

SUMMARY

One hundred and twenty-three cases of leukemia are reviewed. This represents 0.86 per cent of 14,400 consecutive cases in which autopsy was performed at the Cook County Hospital from 1929 to March 1941.

These cases are classified in three ways: (*a*) according to the clinical course, as acute leukemia or chronic leukemia; (*b*) according to the type cell in the peripheral blood, bone marrow and tissues, as stem cell leukemia (28 cases), myelogenous leukemia (53 cases), lymphatic leukemia (37 cases) and monocytic leukemia (5 cases), and (*c*) as leukemic or aleukemic disease. The frequent occurrence (22 per cent) of stem cell leukemia is noted.

The incidence of leukemia with regard to race, sex and age is tabulated and discussed. In our cases 69.9 per cent of the patients were male, 30.1 per cent were female, 78 per cent were white and 22 per cent were colored. The high incidence of acute leukemia in the older age groups is unusual. Stem cell leukemias occurred most frequently in persons in the first three decades.

The symptomatology of leukemic disease is reviewed, and the relative frequency of the symptoms commonly observed in various forms of leukemia is discussed. Previous observations by other authors that acute leukemia of all types presents a typical and almost pathognomonic syndrome can be corroborated.

Enlargement of the liver and the spleen was most commonly encountered in myelogenous leukemia and less frequently in lymphatic leukemia. Generalized lymphadenopathy was the outstanding abnormality in lymphatic leukemia and stem cell leukemia.

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24. Stengel, A., and Pancoast, H. K.: The Treatment of Leukemia and Pseudoleukemia with X-Ray, J. A. M. A. **59**:1166 (Sept. 28) 1912.

25. Minot, G. R., and Isaacs, R.: Lymphatic Leukemia, Age Incidence, Duration and Benefit Derived from Irradiation, Boston M. & S. J. **191**:1, 1924.

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The white blood cell picture showed considerable variability and fluctuation. Attention is drawn to the observation that marked leukopenia may be observed in the early or the late stages of stem cell leukemia and myelogenous leukemia, especially in the acute forms. Marked thrombopenia may cause a hemorrhagic diathesis.

The typical microscopic picture of the liver, the spleen and the lymph nodes is described. "Myeloid metaplasia" was frequently noted in myelogenous leukemia and stem cell leukemia.

Differential counts of bone marrow are compared with those of peripheral blood. The importance of repeated counts is stressed.

The incidence and the distribution of petechial and massive hemorrhages are discussed.

Repeated transfusions of blood were the most beneficial treatment in our cases but gave only temporary relief.

Mount Sinai Hospital (Dr. Preuss).

CLINICAL OBSERVATIONS ON OSTEOPETROSIS AND MYELOFIBROSIS

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There is considerable interest in clinical conditions resembling leukemia or refractory anemia, in which investigation of the bone marrow reveals fibrosis or considerable diminution of the cellular elements. Until recently such conditions were properly identified only at postmortem examination, but at present the frequent use of sternal puncture or biopsy has made it possible to diagnose the condition during life at various stages of its development. According to our clinical observations, the results of microscopic studies on sternal bone and marrow obtained by biopsy and roentgen ray observations, two main disease entities are encountered. These are (1) osteopetrosis (Albers-Schönberg disease, or marble bone disease) and (2) myelofibrosis (myelosclerosis, leukoerythroblastic anemia, myelophthisic anemia, osteosclerotic anemia or nonleukemic myelosis). It is the purpose of this communication to report a case of osteopetrosis and 17 cases of myelofibrosis, in all except 4 of which the diagnosis was made during life.

The disease process known as osteopetrosis (a term suggested by Karshner [1] in 1926 and meaning "stony bone") was first described by Albers-Schönberg [2] in 1904, and since then about 125 cases have been reported.[3] The diagnosis can be made specifically by roentgenograms. The entire osseous system is markedly and usually uniformly dense to roentgen rays (fig. 1). The periosteum as discerned in roentgenograms is intact, but transverse striations of different degrees of density and multiple fracture sites are frequently observed in the shafts of the bones. The generalized condensation of bone found in osteopetrosis cannot be confused with the isolated or scattered condensations of bone present in such conditions as osteopoikilosis,[4] condensing osteitis, eburnizing osteitis, melorheos-

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Dr. Erf is now at the Jefferson Medical College Hospital, Philadelphia.

From the medical services of Dr. George Baehr and Dr. B. S. Oppenheimer and the Laboratories of the Mount Sinai Hospital.

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tosis, fluorine sclerosis [5] and related disorders. Osteopetrosis may be associated with other diseases, as in a case of Hodgkin's disease reported by Hersker and Stein.[6]

Osteopetrosis is frequently found during childhood, and the severe types are characterized by mental and physical retardation; weakness; atrophy of the optic nerve; hydrocephalus; poor dentition; progressive enlargement of the spleen, liver and lymph nodes; progressive development of a refractory type of anemia (associated usually with thrombopenia or leukopenia and often with slight myelemia), and occasionally by osteomyelitis and pathologic fractures. A symptomless type [7] has also been described. This condition remains unrecognized until roentgenograms are taken for other reasons. It has familial and hereditary features, and a history of consanguinity is frequent. The causation remains unknown. Karshner [1] stated the belief that the process is a primary hereditary dyscrasia of mesenchyme, and McCune and Bradley,[3g] that it is an abnormality of the parental germ plasma. Osteopetrosis has been diagnosed in fetuses and in adults as late as the eighth decade. The prognosis varies; the patient may live a few weeks or many decades. The postmortem observations vary, but the usual pathologic changes observed have been those of hepatosplenomegaly; occasionally lymphadenopathy and very dense bone (markedly resistant to sawing in most cases) have been seen, with a small or no medullary cavity. Microscopically the spleen, liver and lymph nodes are often diffusely fibrotic, and occasionally extramedullary hemopoiesis is present. The endosteum of most of the bones reveals a marked increase in the number and thickness of the trabeculae, which encroach on the marrow cavity, often to its exclusion. The periosteum may be involved too. The few spaces which may remain are usually filled with fibrous tissue or large cells resembling reticulum cells and only small deposits of hemopoietic tissue.

Myelofibrosis was first reported by Hueck [8] in 1879. Ante mortem his patient was known to have splenomegaly, leukocythemia and anemia, and post mortem, fibrosis of the spleen with foci of extramedullary hemopoiesis associated with myeloid hyperplasia and generalized fibrosis of the bone marrow. He felt that the patient had had two diseases, myeloid leukemia and osteosclerosis. Since 1879 there have been approximately 75 cases of this disease reported, the diagnosis having been made mainly post mortem. Most of these cases have been reviewed and discussed by Mozer,[9] Chapman,[10] Vaughan [11] and Carpenter and Flory.[12] Generalized fibrosis of the bone marrow and hyperplasia of the endosteum are the predominating pathologic features of this disease. The fibrosis may involve only the marrow cavity, or it may invade the endosteum, the cortex and even the

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periosteum. Scattered and even fairly widespread fibrosis of the marrow may be an associated finding in many disorders, such as atypical Paget's disease,[13] neoplastic osteal processes, bony metastases of prostatic carcinoma,[14] myeloma,[15] septicemia,[9] benzene poisoning and radiation poisoning.[16] The fibrotic changes in myelofibrosis may, however, be primary and recognized during life.

Myelofibrosis is clinically characterized by weakness, dyspnea, refractory anemia, splenomegaly, periostitis and bone pains which frequently are "deep seated" (in the back and lower extremities). It occurs equally often in the two sexes and may be evident at birth or in late adult life. There are no familial or hereditary characteristics known. The prognosis for survival varies from five to six weeks when the disease is acute to several years when it is chronic. The causation is unknown.

The cellular changes of the peripheral blood of patients with myelofibrosis and those with osteopetrosis are frequently similar. The peripheral blood picture resembles occasionally that of chronic myeloid leukemia, but more often that of a refractory type of anemia associated with leukopenia, thrombopenia and the presence of a few immature erythroid and myeloid cells. Various workers[17] have described the same hematologic picture in patients with carcinomatosis, myelomatosis, "spent" polycythemia and megakaryocytic hepatosplenomegaly. The end stage of polycythemia resembles that of the primary disease, whereas megakaryocytic hepatosplenomegaly associated with more or less myelofibrosis may be an early stage or a late stage of the condition. The disease must be differentiated from leukemia, aplastic anemia, Gaucher's disease, Banti's disease, myeloma, osteitis fibrosis cystica, syphilis, skeletal metastases (especially carcinoma of the prostate), osteoplastic cancer, osteomyelitis, radiation osteitis, sclerosis of phosphorus or fluorine poisoning, periosteitis, malaria, Hodgkin's disease and amyloid disease.

The postmortem observations are usually hepatosplenomegaly and occasionally generalized lymphadenopathy, a sclerotic or fibrotic marrow and sclerosis or rarefaction of the osseous system. Microscopically, the spleen, liver and lymph nodes often show chronic inflammatory changes with fibrosis, myeloid hyperplasia and extramedullary erythropoiesis. The marrow cavity may be filled diffusely with fibrous tissue, or there may be areas of hemopoietic tissue interspersed in the fibrous tissue. The endosteal bony trabeculations are usually increased in size and number.

The disease in the cases reported in this communication was identified mainly during life (except in cases 5, 6, 14 and 15) and presented the following clinical classifications:

1. Osteopetrosis (Albers-Schönberg, or marble bone, disease).
2. Myelofibrosis (myelosclerosis, leukoerythroblastic anemia, osteosclerotic anemia).

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A. With refractory anemia without roentgenographic changes of the osseous system.

B. With associated myelemia.

(*a*) Leukopenia or normal white blood cell levels without roentgenographic changes of the osseous system.

(*b*) Leukopenia or normal white blood cell levels with roentgenographic changes.

(*c*) Leukocythemia without roentgenographic changes.

(*d*) Leukocythemia with roentgenographic changes.

Fig. 1 (case 1).—Osteopetrosis; diffuse density of the bones.

C. With associated "spent" polycythemia.

(*a*) Without roentgenographic changes of the osseous system.

(*b*) With roentgenographic changes of the osseous system.

A summary of the observations in the cases of myelofibrosis are presented in the accompanying table.

1. OSTEOPETROSIS (ALBERS-SCHÖNBERG, OR MARBLE BONE, DISEASE)

CASE 1.—*History and Examination.*—B. K., an 18 month old boy, was observed in the consultation service on Dec. 2, 1937. There was a history of retarded physical and mental development, a progressive enlargement of the spleen and liver and an associated progressive pallor. The patient was a thin, pale, inactive child with a prominent abdomen. The edge of the liver was felt 6 cm. below the right costal margin and the edge of the spleen 3 cm. below the left costal margin.

The blood count was: red cells 2,430,000, white cells 16,250, and platelets 80,000. The differential count was: nonsegmented neutrophils 15 per cent, segmented neutrophils 24 per cent, neutrophilic myelocytes 6 per cent, myeloblasts 6 per cent, basophils 1 per cent, lymphocytes 44 per cent, monocytes 4 per cent, erythroblasts 11 per hundred white cells, normoblasts 8 per hundred white cells and reticulocytes 10 per cent. There was 44 per cent hemoglobin. The results of the urinalysis and the Takata-Ara and Wassermann tests were negative. Chemical examination of the blood revealed: phosphorus 6 mg., calcium 11.2 mg. and sugar 80 mg. per hundred cubic centimeters; phosphatase 12.6 King-Armstrong units; serum albumin 4.4 per cent, and globulin 2.7 per cent. On roentgenographic examination all of the bones showed the typical diffuse and severe density. Roentgenograms of the long bones (fig. 1) had no shadows representing medullary cavities, but transverse striations and old fracture sites were present.

Sternal Puncture.—A sternal puncture was attempted, but because of the inability to penetrate the outer plate of the sternum with the aspiration needle a tentative diagnosis of osteopetrosis was made. The diagnosis was confirmed later by roentgenograms of the osseous system.

Course.—The child transitorily improved after transfusions, but in general the clinical course was unsatisfactory.

2. MYELOFIBROSIS (MYELOSCLEROSIS, LEUKOERYTHROBLASTIC ANEMIA, OSTEOSCLEROTIC ANEMIA)

A. MYELOFIBROSIS WITH REFRACTORY ANEMIA WITHOUT ROENTGENOGRAPHIC CHANGES OF OSSEOUS SYSTEM

CASE 2.—*History.*—I. C., a white girl aged 4 months, was admitted to the hospital service of Dr. Schick, on Jan. 3, 1926. A history of a normal delivery was obtained. The child appeared normal at birth and was breast fed for two months. A supplement of cow's milk was given during the following two months. The patient gained weight until two weeks previous to admission. At that time she began to lose her appetite and became weak, inactive, pale and constipated. An irregular elevation of temperature was noted. There were no hemorrhagic tendencies.

Physical Examination.—The patient was moderately well nourished, with marked pallor. The spleen and the liver were barely palpable. Many small shotty cervical lymph nodes could be palpated. The reactions to Wassermann and tuberculin tests were negative and the results of urinalyses normal. Roentgenograms of the thorax and of the long bones were normal. The value for hemoglobin was 20 per cent, for red blood cells 1,120,000, for white blood cells 10,000 and for platelets 150,000. The differential count was: polymorphonuclear neutrophils 40 per cent, neutrophilic myelocytes 3 per cent, myeloblasts 1 per cent, lymphocytes 53 per cent, monocytes 3 per cent, megaloblasts 1 per hundred white cells, normoblasts 2 per hundred white cells and reticulocytes 4 per cent.

Biopsy.—The marrow of the right tibia was markedly fibrotic and was infiltrated with lymphoid cells.

Course.—Four transfusions failed to increase the hemoglobin level, and the child died thirty days after admission. Permission for autopsy could not be obtained.

CASE 3.[18]—*History.*—E. G., a white girl 4 months of age, was admitted to the Beth Israel Hospital,[18] Newark, N. J., on Nov. 11, 1933 with a history of pallor, anorexia and vomiting of one month's duration. The patient was a full term child, normally delivered, having a birth weight of 7 pounds and 13 ounces (3,534 Gm.). She took nourishment well and gained weight for the first three months. The onset of symptoms was gradual, without the accompaniment of fever or hemorrhage.

Examination.—The patient was well developed but pale and lay listlessly in bed. The spleen and the liver were barely palpable. Roentgen examination of the chest revealed an ovoid heart, suggestive of a cardiac anomaly. The skeletal system had no abnormalities roentgenologically.

The blood count showed: red cells 1,050,000, white cells 7,100 and platelets 240,000, with a differential count of polymorphonuclear neutrophils 5 per cent, metamyelocytes 1 per cent, lymphocytes 86 per cent and monocytes 8 per cent. There was 16 per cent hemoglobin. The result of a fragility test of red blood cells was normal. The bleeding time and the coagulation time were within normal limits.

18. Dr. Rosenberg of the pediatric service of Beth Israel Hospital gave permission to publish this case.

Summary of Findings in Cases of Myelofibrosis

Case	Sex	Age	Palpable Enlargement of Spleen	Palpable Enlargement of Liver	Palpable Enlargement of Lymph Nodes	Hemoglobin, %	Red Blood Cells, Thousands per Cu. Mm.	White Blood Cells, per Cu. Mm.	Myelocytes and Myeloblasts in Peripheral Blood	Normoblasts in Peripheral Blood	Results of Marrow Biopsy	Roentgen Changes in Osseous System	Changes in Marrow Seen at Autopsy
A. With Associated Refractory Anemia, but Without Roentgenographic Changes of the Osseous System													
2	F	4 mo.	Slight	Slight	Shotty	20	1,120	10,000	Occ.	Occ.	Tibia: fibrosis with infiltration of lymphoid cells	Normal	No autopsy
3	F	4 mo.	No	No	No	16	1,050	7,100	Occ.	No	Tibia: extensive fibrosis	Normal	No autopsy
4	F	10 yr.	Yes	Yes	Yes	12	1,090	1,900	No	No	Tibia: moderate fibrosis	Normal	No autopsy
B. With Associated Myelemia													
(a) Leukopenia or Normal White Blood Cell Levels Without Roentgenographic Changes of the Osseous System													
5	F	16 mo.	Yes	Yes	Yes	22	1,500	1,700	Yes	Occ.	No	Normal	Generalized fibrosis of marrow
6	F	53 yr.	Yes	Yes	Yes	72	4,170	9,800*	Yes	Occ.	No	Normal	Generalized fibrosis of marrow
7	M	59 yr.	Yes	Yes	Yes	75	4,224	7,600	Yes	Yes	Sternum: diffuse fibrosis	Normal	No autopsy
8	M	55 yr.	Yes	No	No	30	2,050	2,900	Yes	Yes	Sternum: marked fibrosis	Normal	No autopsy
9	M	52 yr.	Yes	No	No	78	4,100	7,200	Yes	Yes	Sternum: moderate fibrosis	Normal	Patient still under observation
(b) Leukopenia or Normal White Blood Cells with Roentgenographic Changes of the Osseous System													
10	F	67 yr.	Yes	Yes	No	38	2,260	4,400	Yes	Yes	Sternum: diffuse fibrosis	Osteoporosis of many bones	No autopsy
11	M	53 yr.	Yes	No	No	52	3,860	4,000	Yes	Yes	Sternum: marked fibrosis	Periosteum of femur split laterally	
12	M	25 yr.	Yes	No	No	56	3,750	8,800	Yes	Yes	Sternum; marked fibrosis	Rarefaction of all bones	No autopsy
13	F	53 yr.	Yes	Yes	No	58	3,670	5,000	Yes	Yes	Sternum: focal fibrosis	Osteoporosis and sclerosis	Patient still under observation
(c) Leukocythemia Without Roentgenographic Changes of the Osseous System													
14	M	40 yr.	Yes	No	Yes	34	3,450	227,000	Yes	Occ.	No	Normal	Generalized fibrosis of marrows
(d) Leukocythemia with Roentgenographic Changes													
15	M	53 yr.	Yes	Yes	Yes	53	3,100	23,000	Yes	Yes	No	Mottling of all bones	Humeral marrow: diffuse fibrosis
16	M	47 yr.	Yes	Yes	Yes	50	2,930	38,000	Yes	Yes	Sternum: diffuse fibrosis	Mottling of all bones	
C. With Associated "Spent" Polycythemia													
(a) Without Roentgenographic Changes of the Osseous System													
17	F	47 yr.	Yes	Yes	No	69	3,500	10,400	Yes	Yes	Sternum: diffuse fibrosis	Normal	Sarcomatous changes of the marrow
(b) With Roentgenographic Changes													
18	M	56 yr.	Yes	Yes	Yes	56	3,400	8,100	Yes	Yes	Sternum; diffuse fibrosis	Mottling of all bones	No autopsy

* Terminally the white blood count rose to 130,800.

Biopsy.—The tibial bone marrow was markedly hypoplastic, with only a few scattered foci of erythroblasts and myeloblasts present. Fibrosis was extensive and was associated with an excess of bony trabeculae (fig. 2).

Course.—With frequent transfusions and with iron and liver therapy the hemoglobin level rose to 80 per cent. The total white cell count and differential count did not change; 90 per cent of the white cells were lymphocytes. Within three weeks the temperature became elevated in association with bloody stools and jaundice. There was some evidence of pulmonary edema, and the child died on December 26. The final blood count was: red blood cells 3,500,000 and white blood cells 1,900, with lymphocytes 86 per cent and monocytes 14 per cent; the hemoglobin amounted to 49 per cent. Permission for an autopsy could not be obtained.

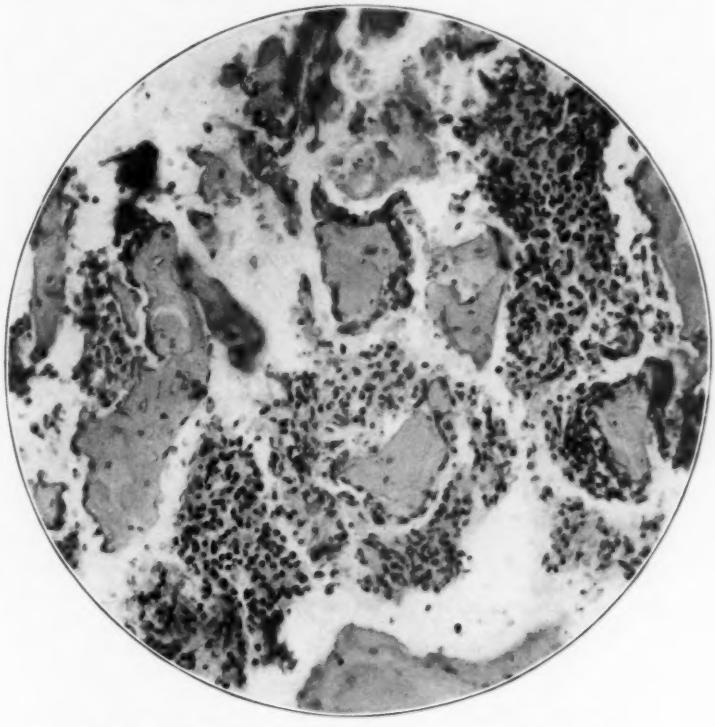

Fig. 2 (case 3).—Tibial bone marrow, showing myelofibrosis.

CASE 4.—*History.*—S. K., a white girl aged 10 years, was admitted to the hospital on Nov. 24, 1929. The past history was irrelevant. The present illness started four weeks before admission, with anorexia, pallor and loss of weight. Two weeks later fever and tarlike stools appeared. On admission the patient had these complaints with the addition of sore throat and puffiness of the tissues about the knees and ankles.

Physical Examination.—The patient was a well developed girl with pronounced pallor, fundal hemorrhages, edema of the ankles and palpable enlargement of the spleen, liver and peripheral lymph nodes. The results of clinical examination of the blood and examination of the stool and urine were normal; cultures of material from the throat were negative. The roentgenograms of the long bones revealed no abnormalities. The hemoglobin content was 12 per cent; the red blood cells numbered 1,090,000 and the white blood cells 1,900, with platelets 12,000, segmented polymorphonuclear leukocytes 3 per cent, lymphocytes 96 per cent and monocytes 1 per cent. A clinical diagnosis of subleukemic lymphatic leukemia was suggested.

Biopsy.—The tibial bone marrow was moderately fibrotic. Some foci of undifferentiated mononuclear cells were present.

Course.—Two transfusions (250 cc. each) were given, and the mucous membrane of the pharynx, which had started to undergo ulceration, improved markedly. Four more transfusions were given but the blood levels did not rise, and the patient died December 30. An autopsy was not permitted.

B. MYELOFIBROSIS WITH ASSOCIATED MYELEMIA

(a) Leukopenia or Normal White Blood Cell Levels Without Roentgenographic Changes of the Osseous System.

CASE 5.—*History.*—D. S., a white girl 16 months old, entered the hospital on July 11, 1922. The child was normal at birth and remained well until she reached the age of 7 weeks. At that time chronic bronchopneumonia developed. Recovery was slow. She had acute gastroenteritis when 3 months old. She vomited daily, and the vomiting was associated with anorexia and loss of weight. Four days before admission the temperature became elevated, with enlargement of the peripheral nodes.

Physical Examination.—The patient was emaciated and had puffy eyelids. There were petechiae on the hard palate. Both the spleen and the liver extended 3½ fingerbreadths below the costal margin. All of the peripheral lymph nodes were enlarged. The results of many chemical analyses of the blood and examinations of the stool and urine were normal. The hemoglobin content was 22 per cent; the red blood cells numbered 1,500,000 and the white blood cells 1,700, with neutrophils 13 per cent, neutrophilic myelocytes 6 per cent, lymphocytes 77 per cent and monocytes 4 per cent. The reaction to a tourniquet test was positive, and the bleeding time was six minutes. The results of roentgen examinations of the chest and upper extremities were normal.

Course.—Transfusions were given without avail. Death occurred on August 1.

Autopsy.—The markedly enlarged liver, spleen and lymph nodes all had a homogeneous appearance on cut section. Microscopically these organs were diffusely infiltrated with myeloid cells and nucleated red cells. The bone marrow was largely replaced by fibrous tissue.

CASE 6.—History.—M. D., a white woman 53 years old, was admitted to the hospital on May 5, 1920. She had had an oophorectomy in 1914 but otherwise had been in good health until six weeks previous to admission, when a constant severe localized pain developed in the upper left quadrant of the abdomen. It was not affected by eating and was not accompanied by nausea or vomiting. She complained, however, of weakness and anorexia.

Physical Examination.—The patient was a well developed, undernourished woman with moderate pallor. The spleen was tender and extended 2 cm. below the left costal margin; the liver extended 3 cm. below the right costal margin. A few small inguinal glands were palpable. The Wassermann reaction was negative. There was no free hydrochloric acid in the stomach contents; the total acidity amounted to 16. The blood urea was 17 mg. and the cholesterol 522 mg. per hundred cubic centimeters. The basal metabolic rate was normal. The results of roentgen examination of the gastrointestinal system, osseous system and genitourinary tracts were normal. The hemoglobin content of the blood was 72 per cent; the red blood cells numbered 4,170,000, the white blood cells 9,800 and the platelets 250,000, with a differential count of neutrophils 68 per cent, neutrophilic myelocytes 13 per cent, myeloblasts 5 per cent, eosinophils 1 per cent, lymphocytes 10 per cent and monocytes 2 per cent. A diagnosis of leukopenic myeloid leukemia was made.

Course.—The patient was discharged and referred to the hematology clinic, which she attended regularly for eight years. Roentgen therapy and solution of potassium arsenite U. S. P. were occasionally given during that period. The blood count did not change until January 1927 (seven years after the first admission), when there was an increase in the total white cell count to 17,600. A year and a half later, June 1928, the white cell count rose to 22,000. The spleen and liver gradually increased in size. Dyspnea occurred on exertion. Because of these gradual changes and the loss of general strength, the patient was readmitted on August 28. Bronchopneumonia in the lower lobes of both lungs was discovered. The results of roentgen examination of the ribs and bones of the upper and lower extremities were normal. The spleen extended to the iliac crest, and the liver extended to the level of the umbilicus. The blood count was: red cells 2,850,000, white cells 124,000 and platelets 100,000, with neutrophils 80 per cent, neutrophilic myelocytes 10 per cent, myeloblasts 3 per cent, eosinophils 3 per cent, lymphocytes 2 per cent, monocytes 2 per cent and normoblasts 24 per hundred white cells. There was 57 per cent hemoglobin. After a transfusion the patient improved. Three weeks later cardiac decompensation developed suddenly, and the patient died on September 18.

Autopsy.—The essential microscopic observations were: coronary sclerosis, fatty and myeloid infiltration of the liver, myeloblastic infiltration of the splenic sinuses and vascular degeneration of the kidneys. Most of the bone marrow was replaced by bony trabeculae and fibrous tissue, and there were few foci of myelocytes or myeloblasts.

CASE 7.—*History.*—P. G., a white man 59 years old, was admitted to the hospital on June 28, 1926. In 1919 he had been informed by his family physician that he had an enlarged spleen. Six months before admission he noted increasing generalized weakness, an increasing deep-seated pain in the lower part of the back and a tumor in the left upper quadrant of the abdoman. His friends noted that his complexion had become yellowish.

Physical Examination.—The patient was well nourished, icteric and afebrile. The liver was firm and extended 4 fingerbreadths below the costal margin and the spleen 6 cm. below the left costal margin. The peripheral nodes were enlarged. The urine was normal except for large quantities of urobilin. The result of a bromsulphalein test was normal. Examination of the blood showed: urea 26 mg. and uric acid 6.2 mg. per hundred cubic centimeters; hemoglobin 75 per cent; red cells 4,224,000, white cells 7,600 and platelets 210,000, with neutrophils 55 per cent, neutrophilic myelocytes 3 per cent, myeloblasts 3 per cent, eosinophils 4 per cent, basophils 5 per cent, lymphocytes 27 per cent, monocytes 3 per cent and megaloblasts 2 per hundred white cells. A diagnosis was made of leukopenic myeloid leukemia with hepatic and renal infiltrations.

Biopsy.—The sternal marrow was diffusely fibrotic. A few islands of myeloid cells were present.

Course.—The patient attended the hematologic outpatient department regularly for two years after his discharge. He showed little change except that on April 25, 1928 the basal metabolic rate was —17 per cent. He was given thyroid, and on his second admission, one year later, on April 8, 1929, the basal metabolic rate was +20 per cent. At this time he complained of progressive weakness and dyspnea. The spleen filled two thirds of the abdomen. The hemoglobin content was 47 per cent; the red blood cells numbered 2,380,000, the white blood cells 5,800 and the platelets 180,000, with neutrophils 54 per cent, neutrophilic myelocytes 3 per cent, neutrophilic eosinophils 2 per cent, neutrophilic basophils 1 per cent, myeloblasts 2 per cent, eosinophils 4 per cent, basophils 5 per cent, lymphocytes 25 per cent and monocytes 4 per cent. Roentgen examinations of the ribs and bones of the upper extremities gave normal results. The patient was discharged from the hospital unimproved. He had a gradual down-hill course and died in 1936, seventeen years after the onset of his disorder. Permission for an autopsy was not obtained.

CASE 8.—*History.*—H. C., a white man aged 55, complained of marked precordial pain and dyspnea. He was first seen on Feb. 27, 1939. He had been known to have syphilis and had received many courses of antisyphilitic treatment. After the last course he complained of the aforementioned symptoms.

Physical Examination.—The patient was well developed, well nourished, pale and dyspneic. The spleen extended 2 fingerbreadths below the left costal margin. The liver was not palpable. There was no lymphoadenopathy. Petechiae were present in the skin and mucous membranes. The hemoglobin content of the blood was 30 per cent. The red blood cells numbered 2,050,000, the white blood cells 2,900 and the platelets 40,000, with polymorphonuclear leukocytes 65 per cent, myelocytes 4 per cent, myeloblasts 3 per cent, eosinophils 1 per cent, lymphocytes 23 per cent, monocytes 4 per cent, normoblasts 3 per hundred white blood cells and reticulocytes 2 per cent. The icterus index was 2. The Kahn reaction was 4 plus. Coagulation time was ten minutes. Roentgen examination of the osseous system showed nothing abnormal.

Biopsy.—The sternal marrow was markedly fibrotic.

Course.—The patient was at first thought to have aplastic anemia following neoarsphenamine therapy. The examination of the biopsy specimen showed that such a diagnosis was not correct. Transfusions were given and were followed by temporary improvement. The patient died eleven months after the onset of the symptoms. An autopsy was not permitted.

CASE 9.—*History.*—J. H., a white man aged 52, was admitted to the hospital on April 28, 1933 with a history of weakness and a chronic hacking cough. From then until 1941 the weakness became progressively worse and pallor was more noticeable.

Physical Examination.—The patient was well developed and pale. A firm, nontender spleen extended 3 fingerbreadths below the left costal margin. Neither the liver nor the peripheral lymph nodes were palpably enlarged. There were no petechiae present. The hemoglobin content of the blood was 78 per cent. Examination of the blood showed: red cells 4,120,000, white cells 7,200 and platelets 450,000, with polymorphonuclear leukocytes 65 per cent, myeloblasts 6 per cent, myelocytes 7 per cent, eosinophils 2 per cent, basophils 3 per cent, lymphocytes

12 per cent, monocytes 3 per cent and normoblasts 2 per hundred white blood cells. The Wassermann reaction was negative. Roentgen examination of the osseous system showed nothing abnormal. A sternal puncture in June 1939 showed: white cells 24,000, megakaryocytes 22, myeloblasts 1.6 per cent, neutrophilic myelocytes 28.6 per cent, myelocytic eosinophils 0.3 per cent, nonsegmented polymorphonuclear leukocytes 14.3 per cent, segmented polymorphonuclear leukocytes 38 per cent, polymorphonuclear eosinophils 0.3 per cent, polymorphonuclear basophils 0.3 per cent, hematogones 3.6 per cent, lymphocytes 0.3 per cent, erythroblasts 1.6 per cent and normoblasts 11 per cent. Because the observations on the marrow were unsatisfactory for establishing a diagnosis, a biopsy of the sternum was carried out.

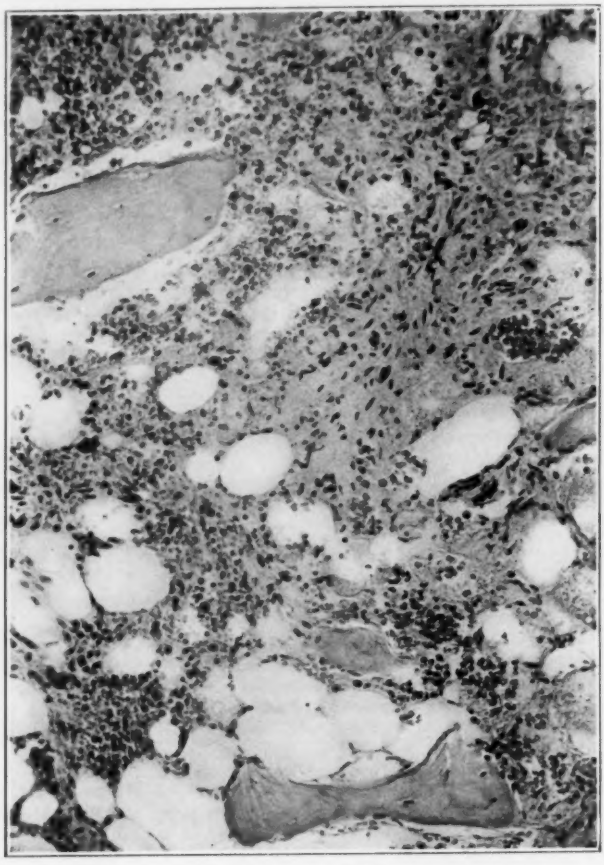

Fig. 3 (case 9).—Early stage of fibrosis of sternal marrow.

Biopsy.—In July 1939 the sternal bone marrow was moderately fibrotic. Increased numbers of megakaryocytes were present and some foci of active hemopoiesis, especially of the erythrocytic series (fig. 3).

Course.—A blood count in June 1940 was as follows: hemoglobin 73 per cent, red cells 4,590,000, white cells 10,000 and platelets 200,000, with myelocytic neutrophils 1.5 per cent, nonsegmented polymorphonuclear leukocytes 10 per cent, segmented polymorphonuclear leukocytes 72 per cent, polymorphonuclear eosinophils 0, polymorphonuclear basophils 0, lymphocytes 11.5 per cent and monocytes 5 per cent. The patient is still under observation at the time of writing.

(*b*) *Leukopenia or Normal White Blood Cell Levels with Roentgenographic Changes of the Osseous System.*

CASE 10.—*History.*—S. G., a white woman 67 years old, was admitted to the hospital in Dec. 2, 1934. She had known for sixteen years that she had an enlarged spleen. For one year previous to admission she complained of gradual progressive weakness, loss of weight and increasing pallor. Ecchymoses, nosebleeds and lumbar pains increased in number and intensity six months before admission.

Physical Examination.—The patient was thin and emaciated, with a yellowish pallor. The spleen extended to the iliac crest. It was smooth, firm, nontender and movable. The liver was firm and extended 8 cm. below the right costal margin. The Wassermann reaction was negative and the icteric index 12. Examination of the blood showed: total proteins 6.4 Gm., sugar 150 mg., cholesterol 150 mg. and cholesterol esters 36 mg. per hundred cubic centimeters; hemoglobin 38 per cent; red blood cells 2,260,000; white blood cells 4,400; platelets 60,000, and a differential count of nonsegmented polymorphonuclear leukocytes 9 per cent,

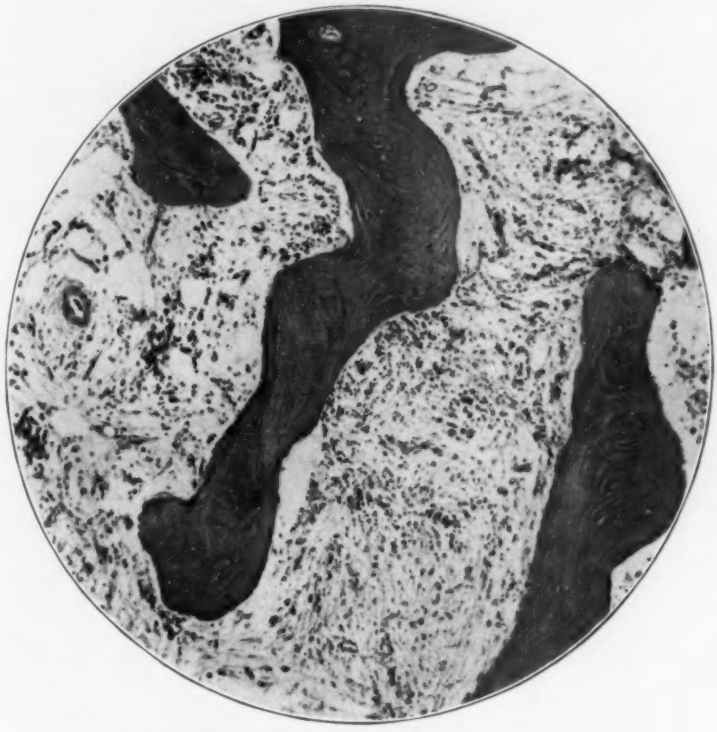

Fig. 4 (case 11).—Diffuse fibrosis of sternal marrow.

segmented polymorphonuclear leukocytes 38 per cent, neutrophilic myelocytes 16 per cent, myeloblasts 4 per cent, lymphocytes 30 per cent, monocytes 3 per cent, normoblasts 17 per hundred white cells and erythroblasts 4 per hundred white cells. As revealed by roentgenologic examination, the femurs were widened above the condyles and had irregular, mottled transparencies in the medulla at this point. The latter characteristic was also observed in the upper third of the femurs and the upper halves of the tibias. There was a generalized osteoporosis of the lumbar vertebrae and pelvic bones.

Biopsy.—Small islands of erythroblasts and myeloblasts scattered throughout an extensive fibrosis were found in place of normal sternal bone marrow.

Course.—The patient was sent to a convalescent hospital after the diagnosis of myelofibrosis was made. Transfusions were given when necessary. She died one year after discharge.

CASE 11.—*History.*—W. E., a white man aged 53, was admitted to the hospital on Jan. 8, 1935. He had been in good health until five years previous to admission, when he noted

weakness, bone pain, especially in the lumbar region and thighs, generalized edema and "heaviness" of the lower extremities. These symptoms gradually increased in severity. Four weeks before the patient's admission pains developed in the right and left upper quadrants of the abdomen, associated with a severe chronic backache.

Physical Examination.—The patient was well developed and pale with slight edema of the face. The spleen extended 3 fingerbreadths below the costal margin. The liver was not palpable. The value for blood proteins was 7 Gm., for blood urea 11 mg., for blood calcium 10.9 mg. and for blood phosphorus 3.8 mg., per hundred cubic centimeters, and that for blood phosphatase was 3.5 Bodansky units. The hemoglobin content was 52 per cent. The red blood cells numbered 3,860,000, the white blood cells 4,000 and the platelets 80,000, with nonsegmented polymorphonuclear leukocytes 13 per cent, segmented polymorphonuclear leukocytes 41 per cent, neutrophilic myelocytes 5 per cent, myeloblasts 1 per cent, eosinophils 1 per cent, basophils 2 per cent, lymphocytes 35 per cent, monocytes 2 per cent, normoblasts 2 per hundred white blood cells and reticulocytes 5 per cent. The cortices of the femurs were split laterally and ventrally, while the remainder of the osseous system was normal roentgenographically.

Biopsy.—During the sternal marrow puncture, a gritty sensation was perceived when the needle entered the marrow cavity, and no marrow could be withdrawn. The sternal biopsy revealed a diffuse fibrosis in the sternal marrow (fig. 4).

Course.—Transfusions were given monthly for over six years, and the patient died eleven years after the first symptoms appeared.

CASE 12.—*History.*—N. G., a white man aged 25, a physician, was admitted to the hospital on June 16, 1936 complaining of fatigue, weakness, pallor, edema of the ankles and pains in the long bones. The nonradiating pains were both dull and sharp. The fatigue and weakness had been complaints of the patient for a year, while the pains in the long bones were of four months' duration.

Physical Examination.—The patient was well developed and apparently chronically ill. A soft blowing systolic hemic murmur was heard over the entire precordium. No enlargement of the liver or of the lymph nodes was discernible on palpation. A firm spleen extended 1 fingerbreadth below the costal margin. On admission the blood count was: red cells 3,750,000, white cells 8,800 and platelets 180,000. The differential count was: nonsegmented polymorphonuclear leukocytes 5 per cent, segmented polymorphonuclear leukocytes 56 per cent, neutrophilic myelocytes 8 per cent, myeloblasts 7 per cent, basophils 5 per cent, basophilic myelocytes 2 per cent, lymphocytes 11 per cent and monocytes 6 per cent, with normoblasts 1 and megaloblasts 1 per hundred white cells. The hemoglobin content was 56 per cent. Areas of rarefaction scattered throughout all the bones except those of the feet and hands were noted on the roentgenograms.

Biopsy.—There was marked fibrosis of the sternal marrow.

Course.—The patient had a chronic elevation of the temperature to between 99 and 100 F. Roentgen therapy was effective in reducing the size of the spleen very slightly. Transfusions and the administration of solution of potassium arsenite U. S. P. and iron were ineffective in raising the hemoglobin level. The white cells varied little in number or quality. The patient's downward clinical course was similar to that of most leukemic patients. An autopsy was not permitted.

CASE 13.—*History.*—M. B., a 53 year old housewife, first noted an enlargement of the spleen in 1930. In 1936 she complained of weakness, nausea and vomiting.

Physical Examination.—The patient was well developed, poorly nourished and pale. The inferior margin of the spleen was within 4 cm. of the iliac crest. In 1936 the blood count was: red cells 3,670,000, white cells 5,000 and platelets 160,000, with nonsegmented polymorphonuclear leukocytes 24 per cent, segmented polymorphonuclear leukocytes 33 per cent, neutrophilic myelocytes 5 per cent, myeloblasts 1 per cent, basophils 1 per cent, lymphocytes 33 per cent, monocytes 3 per cent and normoblasts 1 per hundred white blood cells. The hemoglobin content was 58 per cent.

Sternal Puncture.—Several sternal punctures were made, and few cells were obtained. A tentative diagnosis of myelofibrosis was made.

Course.—In 1937 the patient received injections for varicose veins, following which ulcers of the skin developed. The ulcers failed to heal until 1940. In 1940 the patient was much paler, the spleen extended into the pelvis and the liver extended 6 cm. below the costal margin. The blood findings were almost identical with those of 1936. Roentgenograms of the entire skeleton revealed disorganization of the trabecular structure, with irregular sclerosis of many

bones. The blood phosphatase amounted to 11 King-Armstrong units and the blood calcium and phosphorus to 9.4 mg. and 4.4 mg., respectively, per hundred cubic centimeters.

Biopsy.—A biopsy of the sternum April 1940 revealed focal fibrosis of the marrow and thickening of the bony trabeculae.

Splenic Punctures.—Splenic punctures revealed myeloid metaplasia. Smears appeared not unlike those obtained on sternal puncture, showing immature and mature cells of the myeloid series, normoblasts, erythroblasts and a moderate number of megakaryocytes.

(*c*) *Leukocythemia without Roentgenographic Changes.*

CASE 14.—*History.*—L. B., a white man aged 40, was admitted to the hospital on July 12, 1919. He had been in good health until April 1915, when enlargement of the spleen developed. Roentgen therapy at that time reduced the size of the spleen, and the patient felt better and remained improved until three months before admission. He complained of dimness of vision, dyspnea, night sweats, "burning" in the epigastrium, pain in the left scapular region and gradually increasing pain in the left upper quadrant of the abdomen.

Physical Examination.—The patient was moderately well nourished and pale, with corneal opacities. The spleen extended 2 fingerbreadths below the level of the umbilicus. The liver was not palpable, but the peripheral lymph nodes were. The Wassermann reaction was negative. The blood urea content was 12 mg. per hundred cubic centimeters. The hemoglobin content was 34 per cent. The red blood cells numbered 3,450,000, the white blood cells 227,000 and the platelets 114,000, with a differential count of neutrophils 37 per cent, neutrophilic myelocytes 42 per cent, eosinophils 4 per cent, basophils 10 per cent, lymphocytes 4 per cent and monocytes 3 per cent. On roentgen examination the long bones appeared normal.

Course.—Because of the previous response to roentgen therapy, it was again tried with some success. In ten days the hemoglobin amounted to 71 per cent and the red blood cells numbered 3,480,000 and the white blood cells 7,200, with neutrophils 82 per cent, neutrophilic myelocytes 5 per cent, lymphocytes 9 per cent and monocytes 4 per cent. The patient felt better and left the hospital. He returned three months later, Dec 1, 1919, with the complaints of headache, progressive weakness, vomiting, insomnia, dyspnea, palpitation and tinnitus. The liver was enlarged, extending 1 fingerbreadth below the right costal margin. The spleen and the lymph nodes were enlarged to the size observed on the previous admission. The hemoglobin content was 14 per cent. The red blood cells numbered 1,040,000, the white blood cells 6,400 and the platelets 320,000, with neutrophils 66 per cent, neutrophilic myelocytes 13 per cent, basophilic myelocytes 5 per cent, myeloblasts 5 per cent, lymphocytes 9 per cent and monocytes 2 per cent. The patient did not improve after roentgen therapy and transfusions. He died in December 1919.

Autopsy.—The essential microscopic observations were: generalized fibrosis of the spleen with areas of myeloid hyperplasia and erythropoiesis; passive congestion of the liver with brownish pigmentation in the centers of the lobules and generalized fibrosis of the marrows of the femur, ribs and sternum.

(*d*) *Leukocythemia with Roentgenographic Changes.*

CASE 15.—*History.*—A. S., a white man aged 53, was admitted to the hospital on Oct. 26, 1933. A rather sudden enlargement of the spleen was responsible for a mechanical intestinal obstruction. A splenic artery ligation was the operative procedure considered safest, since the patient had been treated for myeloid leukemia during the preceding four years.

Physical Examination.—The patient was well developed but emaciated and pale, with a huge abdomen and marked edema of the legs. The spleen was hard but mobile; it filled over two thirds of the abdomen. The liver extended 4 fingerbreadths below the right costal margin. Generalized lymphadenopathy existed. Examination of the blood showed: urea 33 mg. and uric acid 3.5 mg. per hundred cubic centimeters, hemoglobin 53 per cent, red cells 3,100,000, white cells 23,000, platelets 310,000 and a differential count of nonsegmented polymorphonuclear leukocytes 40 per cent, segmented polymorphonuclear leukocytes 33 per cent, neutrophilic myelocytes 13 per cent, myeloblasts 5 per cent, eosinophils 2 per cent, lymphocytes 7 per cent and normoblasts 3 per hundred white blood cells. Figure 5 illustrates the giant platelets found in the peripheral blood.

Course.—After a Drösselung operation (a facial constriction of the splenic artery) the blood count changed little, except that the platelets rose to 1,200,000. The postoperative course was uneventful. The patient was discharged on November 30. Within two weeks the spleen decreased in size sufficiently to relieve the obstruction. However, within six months it began to enlarge again. The enlargement this time obstructed the return flow of blood from the lower extremities. The resulting edema of the legs, with gradual progressive generalized weakness plus dyspnea, brought the patient to the hospital to seek relief, on Nov. 22, 1934.

The spleen again filled two thirds of the abdomen. Roentgen therapy was ineffective in reducing the size of the spleen. The blood count was similar to that on the first admission except that megakaryocytic fragments were frequently found in the peripheral blood, 1 per twenty white blood cells. On roentgen examination of the skeletal system a mottling of the vertebrae, ribs, scapulas, clavicles, humeri and iliac bones was noted. Marked ascites developed, and the patient died on December 25.

Autopsy.—A partial autopsy was permitted. The bone marrow of the right humerus was diffusely fibrotic, and scattered throughout were islands of megakaryocytes. The spleen and liver showed the characteristic changes of megakaryocytic hepatosplenomegaly.

Case 16.—*History.*—P. P., a white man aged 47, was admitted on Sept. 14, 1939 complaining of increasing swelling of the abdomen and generalized abdominal pain of five years'

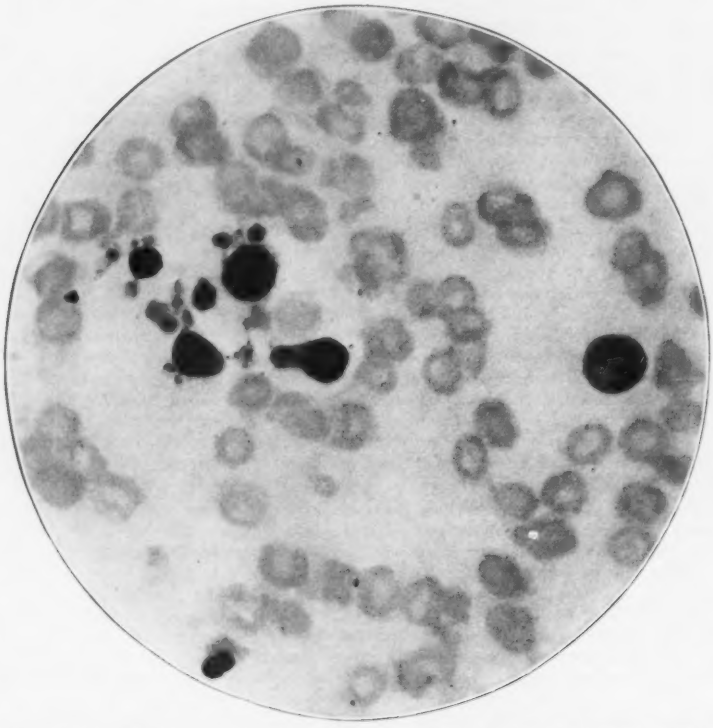

Fig. 5 (case 15).—Blood smear, showing megakaryocytic fragments and giant blood platelets.

duration. Sexual desire had been absent during this period. Two months before admission abdominal distress after meals became severe and dyspnea was marked.

Physical Examination.—The patient was cachectic and had a sallow skin, little hair on any portion of the body and a prominent abdomen. The spleen extended to the iliac crest and the liver to the umbilicus. The hemoglobin content was 58 per cent. The red blood cells numbered 4,080,000, the white blood cells 9,250 and the platelets 150,000, and the differential count showed polymorphonuclear leukocytes 28 per cent, myelocytes 9 per cent, myeloblasts 9 per cent, eosinophils 4 per cent, lymphocytes 36 per cent and monocytes 14 per cent. There were 3 normoblasts per hundred white blood cells, 1.5 per cent reticulocytes and many elliptic and elongated red cells. Chemical examination of the blood showed: uric acid 6.2 mg., cholesterol 140 mg. and calcium 8.3 mg. per hundred cubic centimeters. The Wassermann reaction was negative. The serum albumin amounted to 5.2 Gm. and the globulin to 1.6 Gm. per hundred cubic centimeters. The urine contained no increased excretion of male sex

hormone. Numerous areas of mottling, condensation and rarefaction were noted in the roentgenograms taken of the skull, jaw, vertebrae, humerus (fig. 6) and bones of the hands.

Biopsy.—The sternum had an increased number of bony trabeculae. The normal contents of the marrow were replaced by fibrous tissue in which there were many megakaryocytes (fig. 7). Biopsy of a lymph node revealed chronic lymphadenitis with fibrosis.

Splenic Puncture.—A smear of the aspirated material showed the presence of myeloid metaplasia with numerous myeloblasts, myelocytes and megakaryocytes.

Fig. 6 (case 16).—Numerous areas of mottling and rarefaction.

Treatment.—Pfeiffer and Gardner [19] were able to inhibit experimentally produced myelofibrosis of rats by the administration of testosterone propionate. For this reason testosterone

19. Pfeiffer, C. A., and Gardner, W. U.: Skeletal Changes and Blood Serum Calcium Levels in Pigeons Receiving Estrogens, Endocrinology **23**:485, 1938. Gardner, W. U., and Pfeiffer, C. A.: Skeletal Changes in Mice Receiving Estrogens, Proc. Soc. Exper. Biol. & Med. **37**:678, 1938; Inhibition of Estrogenic Effects on Skeleton by Testosterone Injections, ibid. **38**:599, 1938.

propionate was administered to this patient, who apparently responded favorably for four months. Then there was a rapid decline, clinically, and the patient died on June 6, 1940, before a satisfactory amount of the androgen had been administered.

C. MYELOFIBROSIS WITH ASSOCIATED "SPENT" POLYCYTHEMIA

(a) Without Roentgenographic Changes of the Osseous System.

CASE 17.—*History.*—M. W., a white woman aged 47, was admitted to the hospital on July 10, 1935. This patient had a most interesting past history. When a small girl she was

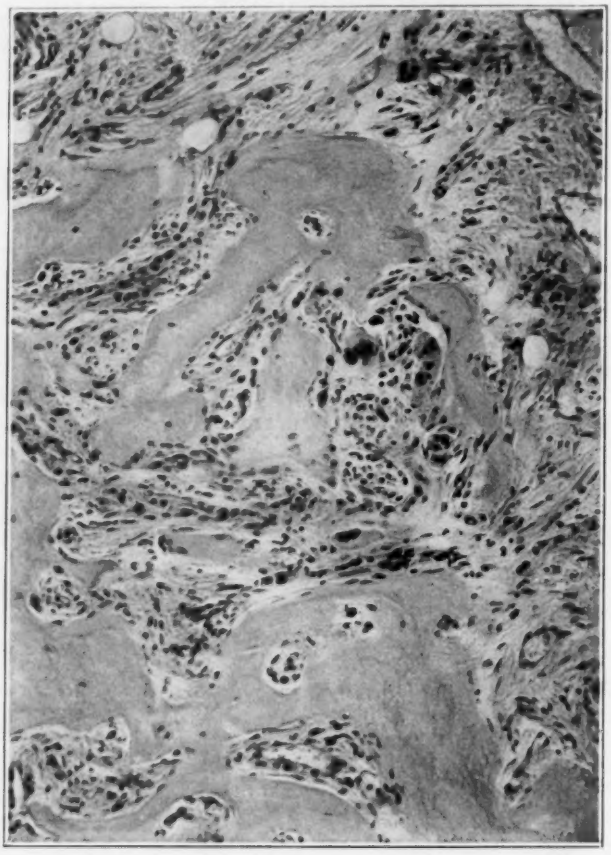

Fig. 7 (case 16).—Sternal marrow showing fibrosis, thickening of the trabeculae and numerous megakaryocytes.

listless, florid and always tired. When 20 years old she had vertigo, headaches and diffuse body aches associated with splenomegaly and an 11,000,000 red blood cell count. Her family physician made the diagnosis of polycythemia (1909). For thirteen years the patient was treated with benzene and roentgen therapy, which controlled her symptoms. For the next ten years she complained constantly of fatigue. The red blood cell count remained within high normal limits until 1935. Three years before the patient's admission (1935) daily chills and fever developed, the origin of which could not be determined. The patient was admitted because of these unexplained episodes of three years' duration and for determination of the cause of the gradual drop in hemoglobin which accompanied them. This case was reported by Rosenthal and Bassen.[17c]

Physical Examination.—The patient was weak and pale, with a flabby musculature, but was fairly well developed and well nourished. The spleen extended 3 fingerbreadths below the costal margin. The liver was just palpable. The basal metabolic rate was — 17 per cent. The blood urea amounted to 15 mg., the blood cholesterol to 310 mg. and the cholesterol esters to 135 mg. per hundred cubic centimeters. The icterus index was 11. Nearly all of the humors, secretions and orifices were examined bacteriologically, without informative results. The hemoglobin was 69 per cent. The red blood cells numbered 3,500,000, the white blood cells 10,400 and the platelets 90,000. The differential count showed nonsegmented polymorphonuclear leukocytes 10 per cent, segmented polymorphonuclear leukocytes 50 per cent, neutrophilic myelocytes 1 per cent, myeloblasts 5 per cent, eosinophils 2 per cent, basophils 1 per cent, lymphocytes 29 per cent, monocytes 2 per cent and normoblasts 2 per hundred white cells. There were marked anisocytosis and poikilocytosis of the red cells, and many elliptic cells were found in the smears. Examinations of stools for parasites gave negative results. All roentgen examinations of the osseous system showed nothing abnormal.

Sternal Puncture and Biopsy.—A gritty, crunchy sensation was noted when the aspiration needle entered the marrow cavity. No marrow fluid could be withdrawn. The sternal marrow removed for biopsy was diffusely fibrotic.

Course.—The patient was discharged with the continuance of the unexplained chills and fever. It was decided that the anemia was a result of a "burnt-out" polycythemic process. The patient attended the hematologic outpatient clinic for injections of liver in an attempt to raise the hemoglobin level. After one of these injections a gluteal abscess developed. Later a chronic sloughing ulcer appeared at the site of the abscess, and a specimen for biopsy removed from the margin showed that the tissue was infiltrated with leukemic cells. The patient died six months after admission to the outpatient department.

Autopsy.—Sarcomatous tissue replaced not only the fibrous tissue of the sternal marrow cavity but the marrow of all the bones. A diagnosis of myelosarcomatosis was made.

(*b*) *With Roentgenographic Changes of the Osseous System.*

Case 18.—*History.*—J. W., a white man aged 56, was admitted to the hospital on Feb. 4, 1931. A diagnosis of polycythemia had been made thirteen years previously because the hemoglobin level was 130 per cent and the red blood cell count was 9,500,000. The complaints at that time were headache, vertigo, abdominal enlargement and a thrombosis of the right middle toe which had become painfully gangrenous. Because of progressive enlargement of the spleen, lumbar pain and bloody urine, the patient was readmitted.

Physical Examination.—The patient was small, thin and sharp featured, with a huge abdomen and small purpuric lesions over the lower extremities. General arteriosclerosis and ascites were present. The spleen extended into the iliac fossa, and the liver extended 2½ inches (6.3 cm.) below the costal margin. The peripheral lymph nodes were palpable. The basal metabolic rate was + 34 per cent. The icteric index was 14. Examination of the blood showed: urea 22 mg., cholesterol 110 mg., sugar 115 mg., calcium 11 mg. and phosphorus 3.7 mg. per hundred cubic centimeters; hemoglobin 56 per cent; red cells 3,400,000, white cells 8,100 and platelets 300,000; neutrophils 59 per cent, neutrophilic myelocytes 5 per cent, myeloblasts 8 per cent, basophils 5 per cent, lymphocytes 15 per cent, monocytes 8 per cent and normoblasts 6 per hundred white blood cells. Roentgenographically, the skull, the left femur, head of the right femur and the pelvic bones had a mottled appearance throughout. In a few areas there were erosions of the cortex of these bones.

Biopsy.—The sternal marrow was diffusely fibrotic. A photomicrograph of this patient has been published.[20]

Course.—The blood in the urine was due to an accumulation of uric acid crystals in the ureters, and the symptoms disappeared after ureteral washings. The patient was discharged feeling considerably better. After a two year downhill course, with gradually increasing anemia, he died suddenly. Permission for an autopsy could not be obtained.

COMMENT

Both osteopetrosis and myelofibrosis are uncommon disorders of unknown causation in which an abnormality within the osseous system, by one means or another, alters or displaces the contained hemopoietic tissue. In the former, the marrow cavity is often obliterated by an overgrowth of abnormal bone, while in the

20. Rosenthal, N.: Aplastic Anemia and Osteosclerosis, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1937, vol. 3, sect. 29, pp. 2201-2230.

latter the hemopoietic tissue is replaced by various degrees of fibrosis. Ischemia of marrow may well be a factor in the development of the hematologic picture in each of these diseases, as it has been shown by Huggins and Wiege [21] that destruction of the nutrient vessels of bones may result in fibrosis of the marrow. According to Kistler,[22] such experimental production of fibrosis is difficult at times.

These conditions have been classified by Vaughan [10] under leukoerythroblastic anemia. This is defined as an anemia not necessarily very severe, characterized by the presence of a few immature white cells of the myeloid series and immature red cells in the peripheral blood. The recognition of this type of anemia during a routine examination of the blood may be the first indication of the existence of some unusual involvement of the bone marrow such as: (1) carcinomatosis with skeletal metastases; (2) myelomatosis; (3) osteosclerosis, including (*a*) marble bone disease and (*b*) myelosclerosis, and (4) Cooley's anemia. With these conditions Vaughan [11] now includes polycythemia vera. A similar anemia was observed by us in association with lipomatosis of the bone marrow.

These conditions may then be recognized, in addition to study of the blood picture, by means of sternal puncture, sternal biopsy, splenic puncture, puncture of lymph nodes and roentgenograms of the bones.

1. The Blood Picture.—The anemia may vary from a hypochromic to a hyperchromic type. The red cells, however, show anisocytosis and poikilocytosis. In the anemic, or "spent," stage of polycythemia and occasionally in primary myelosclerosis (possibly asymptomic polycythemia), many elliptic red cells are present. Normoblasts are found except in rare cases. The blood platelets show pronounced variations. They may be either normal or much reduced in number in the peripheral blood. They also exhibit morphologic variations which are found almost exclusively in myelosclerosis. Some are particularly large, staining with a pale chromomere and pale-staining hyalomere.[23] Giant platelets and megakaryocytic fragments and megakaryoblasts are occasionally found. More marked and bizarre variations have been found after splenectomy by Downey and Nordland.[23a] Likewise, the white blood cells vary in number and type; leukopenia is most often found. It is not unusual to see a pronounced increase in nonsegmented neutrophils and occasionally a few myelocytes and an occasional myeloblast. The myelocytes and occasional myeloblasts may be associated with severe leukocytosis (leukocythemia), as in 4 cases of this series.

2. Sternal Puncture.—This is of primary importance in diagnosis. The density of the sternal bone may be detected by this means. In cases of osteopetrosis the bone is stony and the needle will not penetrate through the cortex, this situation suggesting the diagnosis immediately, especially if it occurs in an infant. The sternal bone in cases of "spent" polycythenia is also dense and yields little marrow. Smears of the marrow reveal only a few cellular elements. The sternal puncture in most cases of myelofibrosis is disappointing. The bone feels gritty on puncture and yields little marrow. In a few cases in which an appreciable amount was aspirated the nucleated cell count was less than that of the peripheral blood. The differential count on the smears showed a normal distribution of leukocytic and erythroblastic elements. The finding of a nonleukemic bone marrow, or failure

21. Huggins, C., and Wiege, E.: Effect on Bone Marrow of Disruption of Nutrient Artery and Vein, Ann. Surg. **110**:940, 1939.

22. Kistler, G. H.: Sequences of Experimental Infarction of the Femur in Rabbits, Arch. Surg. **29**:589 (Oct.) 1934.

23. (*a*) Downey, H., and Nordland, M.: Myeloid Megakaryocytic Hepato-Splenomegaly. Folia haemat. **62**:1, 1939. (*b*) Rosenthal.[20]

to obtain marrow on aspiration in the presence of a leukemic blood picture, should lead one to suspect a fibrotic change in the marrow. This finding led to the diagnosis of myelofibrosis in a case reported by Mavros in 1931. The performance of sternal puncture as a routine measure in all cases of anemia (leukoerythroblastic or otherwise), splenomegaly and leukemia has been responsible for the more frequent detection of myelofibrosis (Vogel, Erf and Rosenthal [24]).

3. Sternal Biopsy.—Sternal puncture is the first step in identification, but biopsy of the sternal bone and marrow is important for conclusive evidence of the underlying myelofibrosis. Of the 17 cases reported in this communication, the diagnosis of myelofibrosis was made in 13 during life and in 4 at autopsy. Likewise, diagnosis of the condition was made during life by the following investigators: Chapman [10] in 2 cases, Fairbank [3b] in 1 case, Stephens and Bredeck [25] in 2 cases and Thompson and Illyne [26] in 5 cases.

4. Splenic Puncture.—Splenic puncture has been suggested by Hirschfeld [17b] and Weil [27] as a means of revealing the myeloid metaplasia which is usually found in myelofibrosis. This was performed in 3 recent cases and revealed the presence of numerous immature cells of both the myeloid and the erythroblastic series. Megakaryocytes were present to a varying degree. In some 27 reported cases reviewed by Hickling,[28] splenectomy was performed without any improvement in the general condition. In some instances numerous megakaryocytes were found in the spleen, leading to the idea of megakaryocytic leukemia. In some of these cases the disease may possibly have been associated with marked hyperplasia of the bone marrow—panmyelosis (Hickling [28]). In other instances, however, this megakaryocytic splenomegaly was associated with fibrosis of various degrees of the marrow, as in the cases of Schwarz,[29] Donhauser,[30] Hewer,[31] Downey and Nordland [23a] and Carpenter and Flory.[12] For this reason it might be considered that the picture in some of these cases conforms to the changes observed in osteosclerotic anemia and that the increase of megakaryocytes in the spleen is a sign of active hemopoiesis or myeloid metaplasia.

5. Lymph Node Puncture.—This was performed in 1 case and revealed a myeloid metaplasia, few megakaryocytes and erythroblasts and many immature myeloid cells scattered among the lymphoid cells. A biopsy of the lymph node also showed a myeloid metaplasia.

6. Roentgen Studies.—A study of the bones is important for confirmatory diagnosis in all cases of osteopetrosis. About 50 per cent of patients with myelofibrosis show on roentgen examination mottled rarefactions or irregular condensations in the cortical portions of the bones and splintering or elevations of the

24. Vogel, P.; Erf, L. A., and Rosenthal, N.: Hematological Observations on Bone Marrow Obtained by Sternal Puncture, Am. J. Clin. Path. **7**:436 and 498, 1937.

25. Stephens, D. J., and Bredeck, J. F.: Aleukemic Myelosis with Osteosclerosis, Ann. Int. Med. **6**:1087, 1933.

26. Thompson, W. P., and Illyne, C. A.: Clinical and Hematological Picture Resulting from Bone Marrow Replacement, M. Clin. North America **24**:841, 1940.

27. Weil, P. E.; Isch-Wall, P., and Perlès, S.: La ponction de la rate, Paris, Masson & Cie, 1936.

28. Hickling, R. A.: Chronic Non-Leukemic Myelosis, Quart. J. Med. **6**:253, 1937.

29. Schwarz, E.: Ein Fall von Leukämie mit Riesenzellemboli und Osteosklerose, Ztschr. f. Heilk. **22**:294, 1901.

30. Donhauser, J. L.: The Human Spleen as an Hematoplastic Organ, as Exemplified in a Case of Splenomegaly with Sclerosis of the Bone Marrow, J. Exper. Med. **10**:559, 1908.

31. Hewer, T. F.: Megakaryocytic Myelosis with Osteosclerosis, J. Path. & Bact. **45**:383, 1937.

periosteum.[32] Von Jaksch [33] in 1901 was the first to demonstrate these changes. Some authors [34] described roentgenologic changes of the bones in their cases, while others [35] presented cases in which roentgen ray changes of the osseous system were not evident. Although in some cases the fibrosis extends from the endosteum to the periosteum, fractures rarely occur.

PATHOGENESIS

The cause of myelofibrosis is unknown. Some authors have suggested that the fibrosis is an aftermath or healing process of leukemia (Neumann,[36] Stephens and Bredeck,[25] Schwarz [29] and Lehndorff and Zak [37]). This is rather doubtful, as the bone marrow even in the earliest stages of myelofibrosis is hypoplastic except in polycythemia and does not show any changes typical of leukemia. Furthermore, the characteristic pathologic changes of leukemia are missing. Hammer, [38] Askanazy [39] and Wade [40] associated myelofibrosis with pseudoleukemia, a condition subject to great controversy. A toxic agent has also been held responsible for the development of the fibrosis (Schmidt,[35b] Donhauser [30] and Wolf [35j]). Lehndorff and Zak [37] and Anagnostu [41] thought the process one of atrophy of the marrow probably due to endogenous or exogenous agents, and recently Pfeiffer and Gardner [19] have demonstrated that estrogenic substances administered in large amounts cause endosteal thickening and fibrosis of the marrow in mice, rats, pigeons and chickens. Silberberg and Silberberg [42] have demonstrated similar changes in immature guinea pigs and Sutro [43] in mice after administration of estrogenic agents.

It seems more plausible, however, that the myeloid metaplasia of the liver and spleen is secondary or compensatory to the loss of marrow function. To some extent the enlargement of the liver and spleen parallels the degree of the fibrosis. The examination of the sternal marrow in the early stages revealed only partial fibrosis, and this was accompanied with a moderate enlargement of the spleen and with less severe clinical symptoms. In cases of chronic, long-standing involvement, from ten to seventeen years in our series, the spleen was greatly enlarged. In cases of acute myelofibrosis, in which this compensatory enlargement of the spleen is not prominent, the symptoms are more severe and the peripheral blood

32. Overgaard, K.: Ein Fall von osteosklerotischer Anämie, Acta radiol. **17**:51, 1936.

33. von Jaksch, R.: Multiple Periostaffection und an myelogene Leukämie mahnender Blutbefund, Prag. med. Wchnschr. **26**:2 and 19, 1901.

34. Chapman.[10] Fairbank.[3b] Stephens and Bredeck.[25]

35. (*a*) Mavros, A.: Aleukämische, besser "nichtleukämische Myelose" mit Osteosclerosis, Folia haemat. **43**:323, 1931. (*b*) Schmidt, M. B.: Ueber osteosklerotische Anämie und Albers-Schönbergsche Krankheit, Beitr. z. path. Anat. u. z. allg. Path. **77**:158, 1927.

36. Neumann, E.: Ueber leukämische Knochenaffectionen, Berl. klin. Wchnschr. **17**:281, 1880.

37. Lehndorff, H., and Zak, E.: Myeloide Leukämie im Greisenalter mit eigenartigen histologischen Befunden, Folia haemat. **4**:636, 1907.

38. Hammer, H.: Primäre sarcomatöse Ostitis mit chronischen Rückfallsfieber, Virchows Arch. f. path. Anat. **137**:280, 1894.

39. Askanazy, M.: Ueber extrauterine Bildung von Blutzellen in der Leber, Verhandl. d. deutsch. path. Gesellsch. **7**:58, 1904.

40. Wade, H. W.: A Preliminary Report on a Case of Hemopoietic Splenomegaly with Marrow Sclerosis, J. Philippine Islands M. A. **1**:143, 1921.

41. Anagnostu, J. L.: Beitrag zum Studium der systematischen Osteosklerosen (Knochenmarksklerose mit leukämoiden Blutbilde), Folia haemat. **50**:70, 1933.

42. Silberberg, M., and Silberberg, R.: Action of Estrogens on Skeletal Tissues of Immature Guinea Pigs, Arch. Path. **28**:340 (Sept.) 1939.

43. Sutro, C.: Effects of Subcutaneous Injection of Estrogen upon Skeleton in Immature Mice, Proc. Soc. Exper. Biol. & Med. **44**:151, 1940.

is less leukemoid. It is felt that there is a reciprocal functional relation between the liver and the spleen, on the one hand, and the bone marrow, on the other. Normally, during fetal life the liver and spleen are hyperfunctioning, while during adult life the bone marrow is the fundamental hematogenetic organ. The degeneration or disappearance of the cells of the bone marrow in myelofibrosis may be due to some reversal of this reciprocal relationship.

This situation is forcibly illustrated by the terminal fibrosis which occurs in polycythemia. The hyperplastic marrow in this disease shows a gradual change over a span of years to one of hypoplasia and generalized myelofibrosis. As these develop there is a gradual increase in the size of the liver and, especially, of the spleen, which usually occupies during the terminal stage the whole left side and part of the right side of the abdomen. As in the primary type of myelofibrosis, there are severe anemia and a leukemoid blood picture.

Vaughan and Harrison [17e] and Carpenter and Flory [12] stated the belief that the condition is due to a progressive hyperplasia of multipotential mesenchymal tissues by an unknown stimulus.

TREATMENT

The treatment of both osteopetrosis and myelofibrosis has been most unsatisfactory. Transfusions have proved to be of only temporary benefit to patients with the chronic types of these disorders. Splenectomy is contraindicated and has not proved of value in the few cases reported.[44] However, recent experimental work has brought new hopes for a treatment of myelofibrosis. Pfeiffer and Gardner [19] showed that estrogenic substances administered in large amounts cause endosteal thickening and fibrosis of the marrow of mice, rats, pigeons and chickens, and they have been able to prevent the experimentally produced disease by the administration of testosterone propionate. Silberberg and Silberberg [42] noted that estrogenic substances administered to immature guinea pigs accelerated the development of the mesenchymal reticulum of bone marrow toward fibrosis, bone formation and megakaryocytosis. Patient 16 was treated with testosterone propionate in an endeavor to inhibit a possible abnormal hyperestrogenic activity. Although there was some hematologic and clinical improvement for a few months after the administration of the glandular substance, the myelofibrotic process had progressed so far as to prevent critical evaluation of the efficacy of the treatment.

SUMMARY AND CONCLUSIONS

The clinical and laboratory observations in 1 case of osteopetrosis and 17 cases of myelofibrosis are discussed.

These conditions may be differentiated from refractory types of anemia, splenomegaly and leukemia by sternal puncture and, conclusively, by sternal biopsy.

Suggestive roentgenologic changes of the bones may be revealed in 33 per cent of the cases.

A practical classification of osteopetrosis and myelofibrosis is presented.

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44. Carpenter and Flory.[12] Downey and Nordland.[23a] Hirsch.[17a]

PROFILE PRINTING IN THE PHOTOMICROGRAPHY OF BLOOD CELLS

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Photomicrography has been used to good advantage for a number of years to record for future reference or for purposes of demonstration the microscopic appearance of blood cells or tissue sections. That it might be used to demonstrate the actual shape of the erythrocyte and the location of granules in the leukocyte seemed possible, particularly after the introduction of the profile or three dimensional method of printing.

The problem which offered the most important possibility was that of demonstrating the spherocytes in the blood of a person suspected of having familial hemolytic anemia. However, in order to do this, it seemed desirable to visualize for comparison the erythrocytes of the blood of normal persons and those with other varieties of anemia.

In figure 1 is shown the photomicrograph of erythrocytes from a normal person as printed in the usual manner for comparison with the same erythrocytes recorded by the profile method, as in figure 2. The biconcave disk shape of normal erythrocytes is well illustrated in the latter. It is also to be noted that the concavity is of rather uniform depth in normal erythrocytes and occupies a rather fixed portion of the cell, leaving a border ring of uniform width and thickness.

The erythrocytes of a patient with hypochromic anemia, as seen in figure 3, show in addition to the characteristic variation in size and shape a concavity of varying depth and extent with a border ring of less than normal thickness. These evidences of insufficient hemoglobin to fill the cells properly are definitely more striking than those in the usual photomicrograph.

The erythrocytes in the blood of the patient with pernicious anemia, as seen in figure 4, show considerable variation in the extent and the depth of the concavity, although the border ring is generally of the same thickness as that of normal blood. In regard to this condition the profile printing has added little of importance to the ordinary photomicrograph but does emphasize the well known fact that the majority of the individual erythrocytes in pernicious anemia are well filled with hemoglobin.

The most striking difference in the photomicrographs prepared by the two methods is found in those of blood from a patient with familial hemolytic anemia. The erythrocytes are shown by the usual method in figure 5 and by the profile method in figure 6. In the latter the so-called spherocytes are seen as slightly convex disks or pill boxes with slightly expanded sides. These are not spheres as the term spherocyte suggests, but because of the definite convexity of their sides they are easily and certainly distinguishable from the biconcave disk of normal blood. Probably no method of demonstrating these cells so accurately or so certainly has been previously presented. This fact should indicate the value of this form of photomicrography as an aid to the diagnosis of familial hemolytic anemia.

From the Medical Service of the Peter Bent Brigham Hospital.

This article was presented as part of a scientific exhibit at the annual meeting of the Massachusetts Medical Society, May 21-22, 1940.

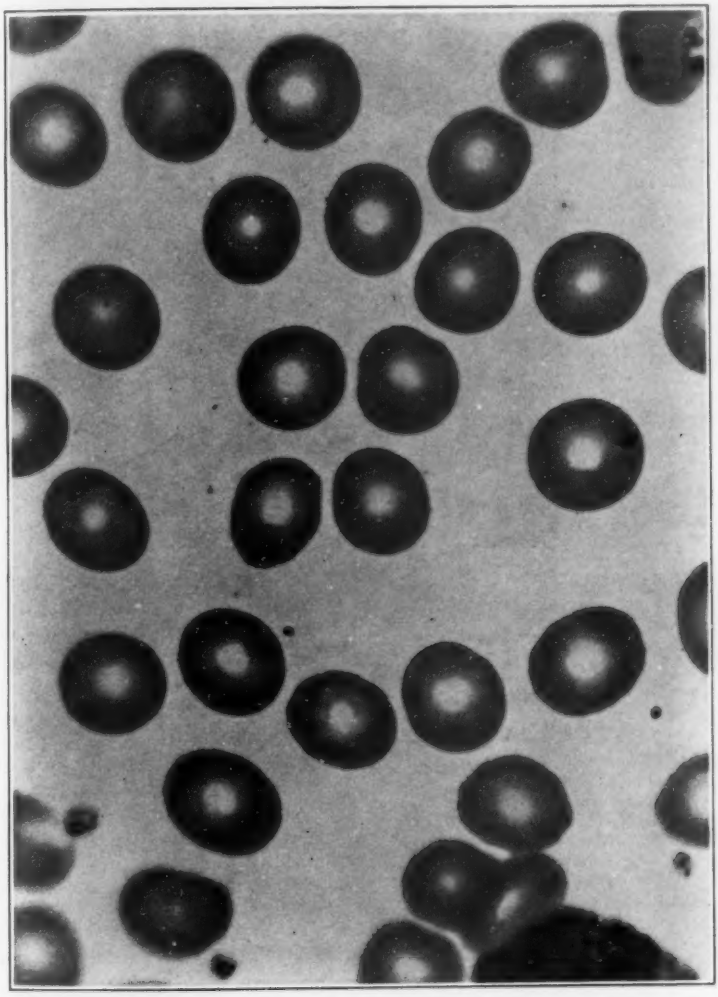

Fig. 1.—Photomicrographs of normal erythrocytes in human blood smear, printed in the usual manner.

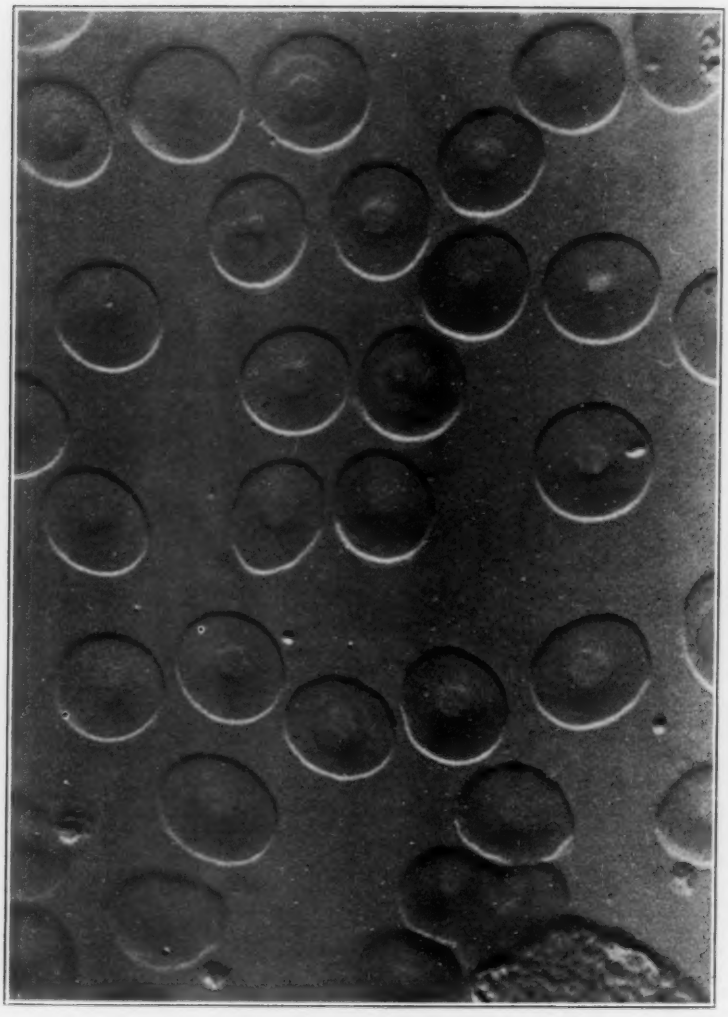

Fig. 2.—The erythrocytes shown in figure 1 as they appear in profile with the three-dimensional method of printing.

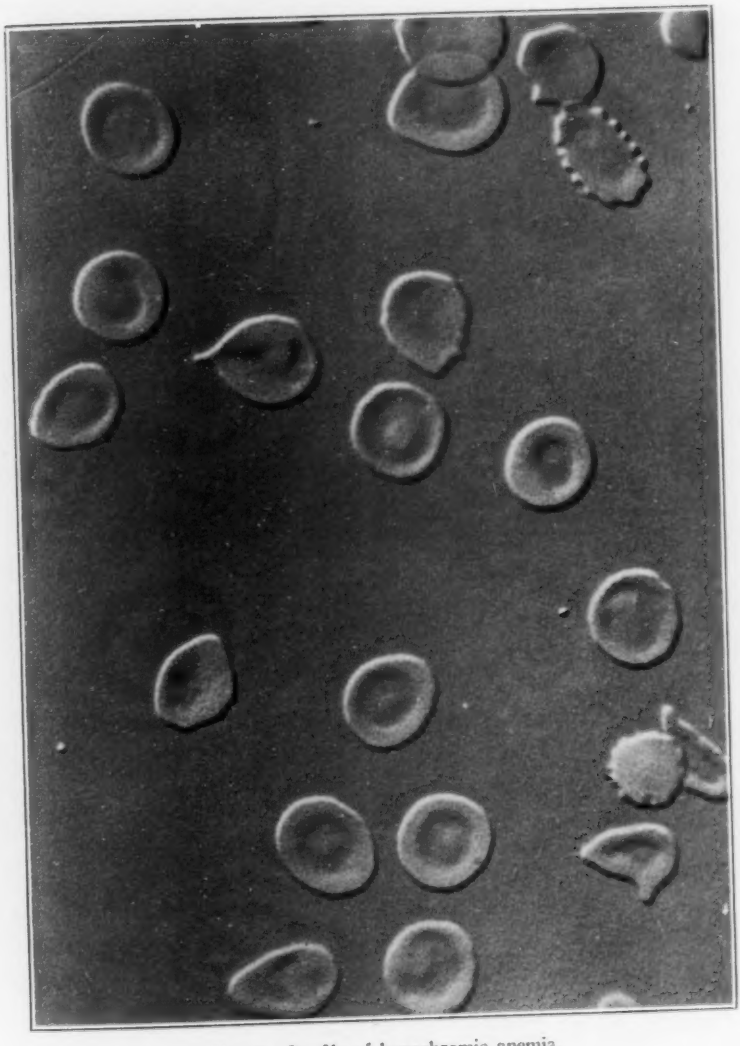

Fig. 3.—Profile of hypochromic anemia.

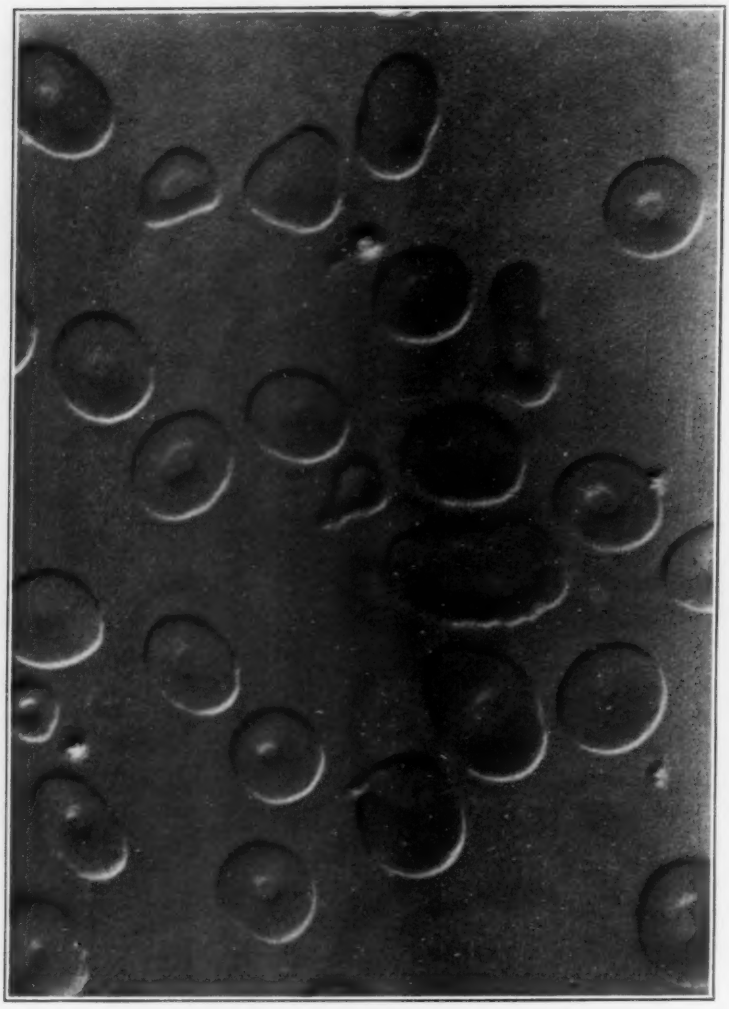

Fig. 4.—Profile of pernicious anemia.

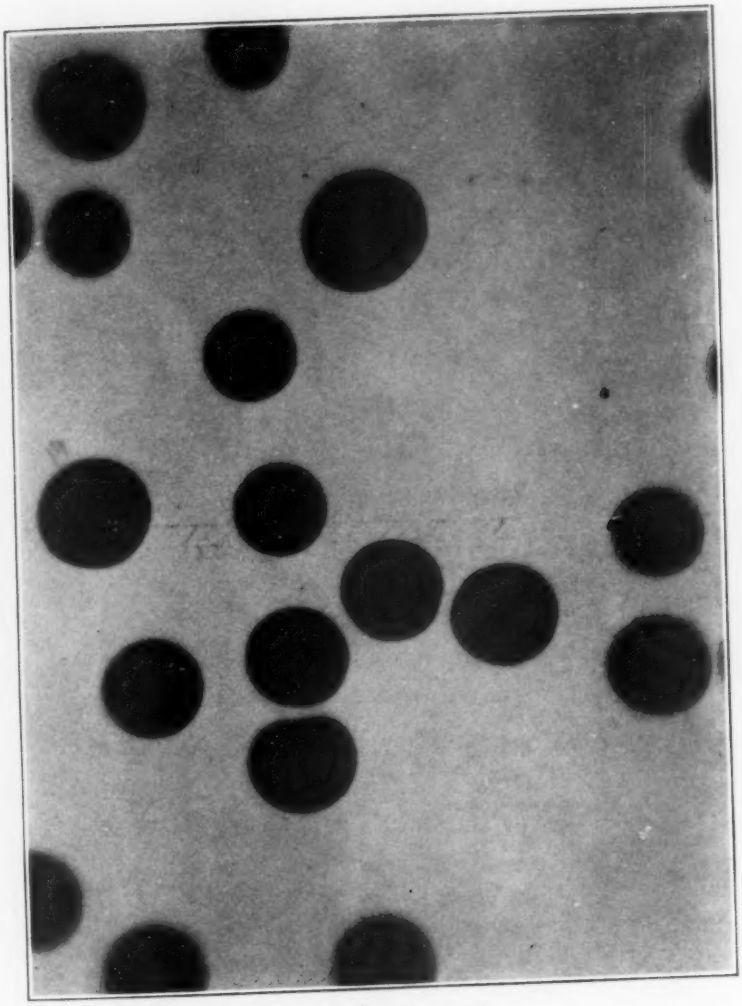

Fig. 5.—Hemolytic anemia.

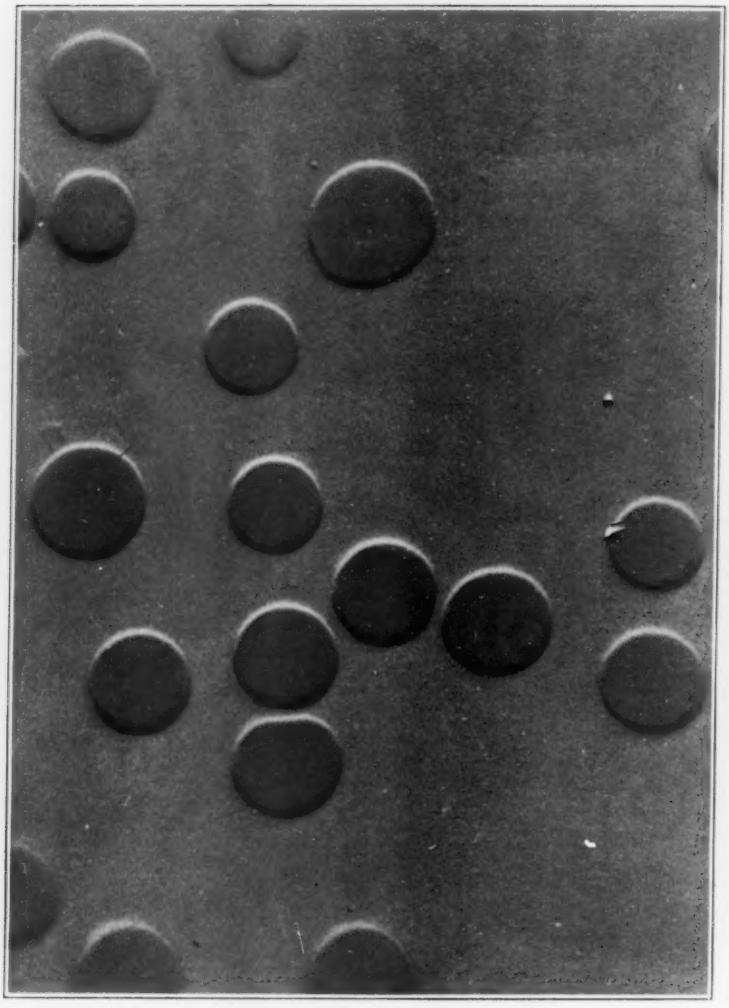

Fig. 6.—Profile of hemolytic anemia.

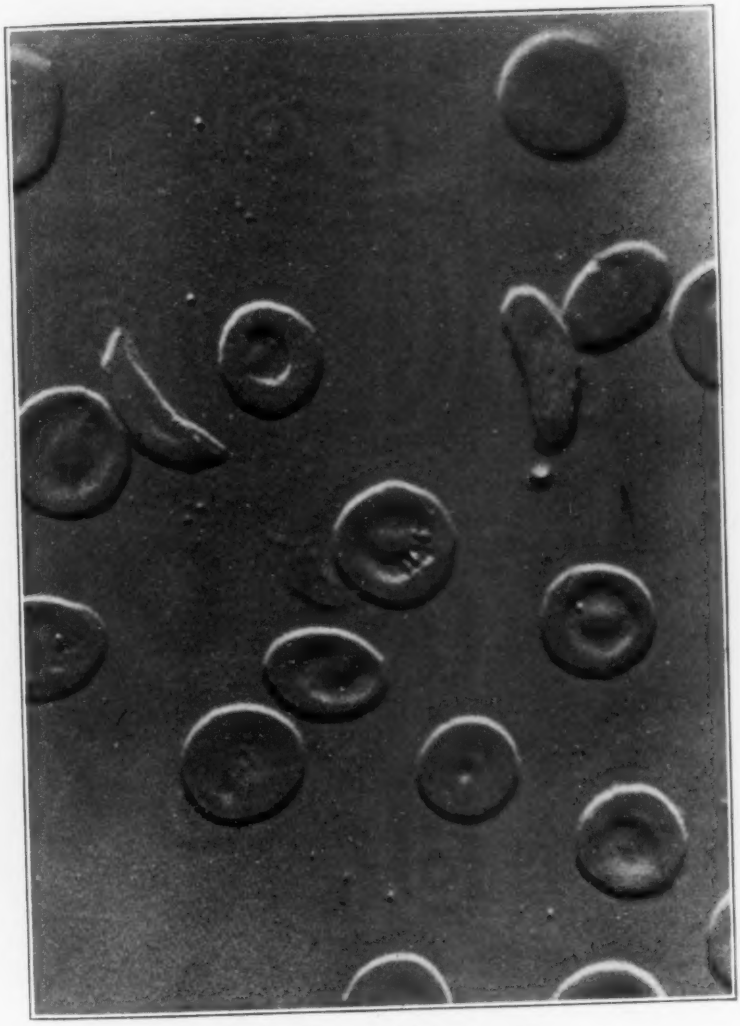

Fig. 7.—Profile of sickle cell anemia.

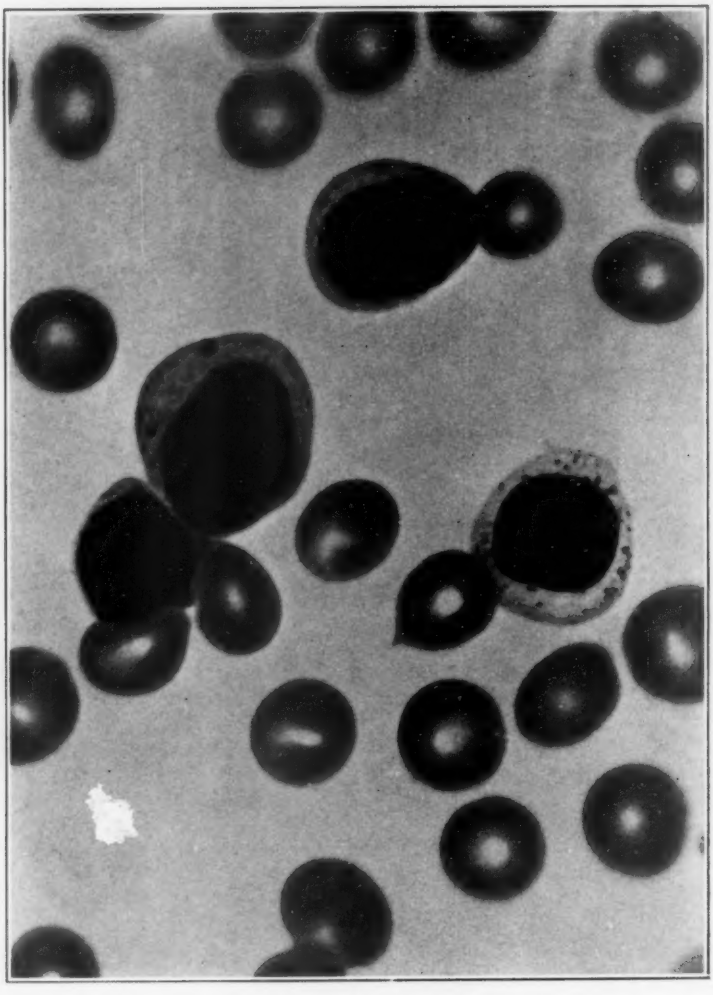

Fig. 8.—Lymphatic leukemia.

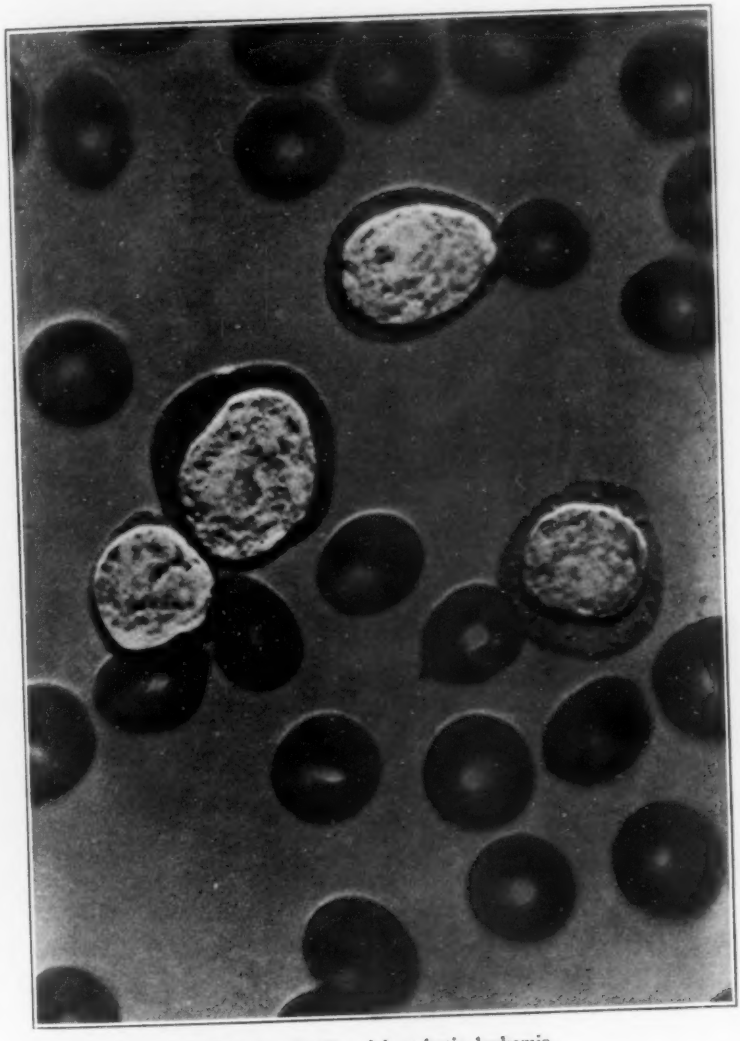

Fig. 9.—Profile of lymphatic leukemia.

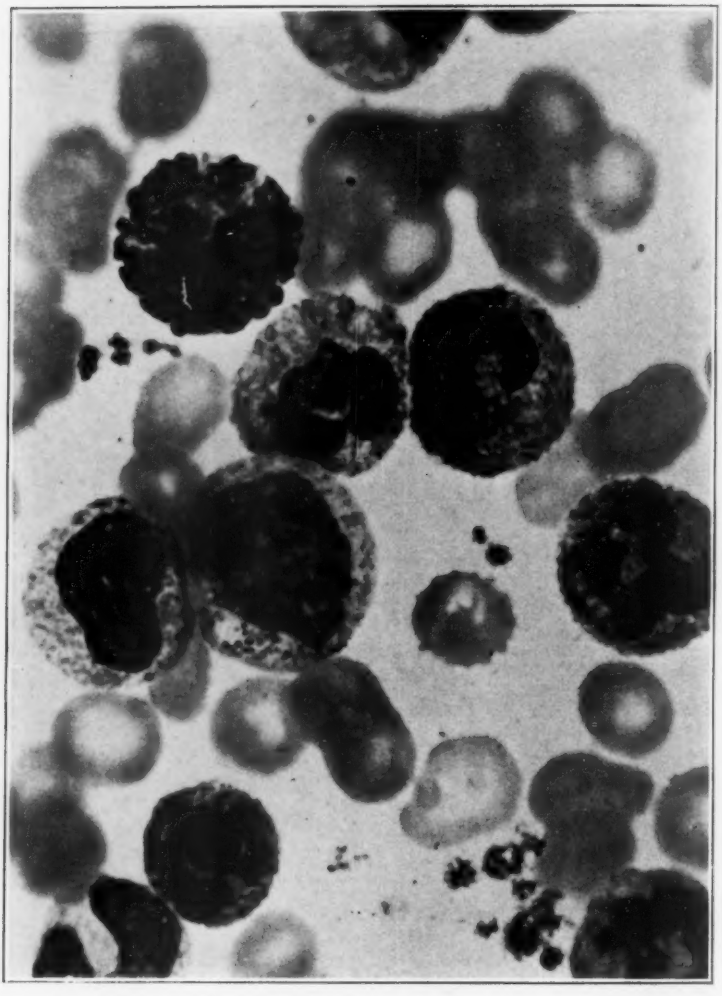

Fig. 10.—Myelogenous leukemia.

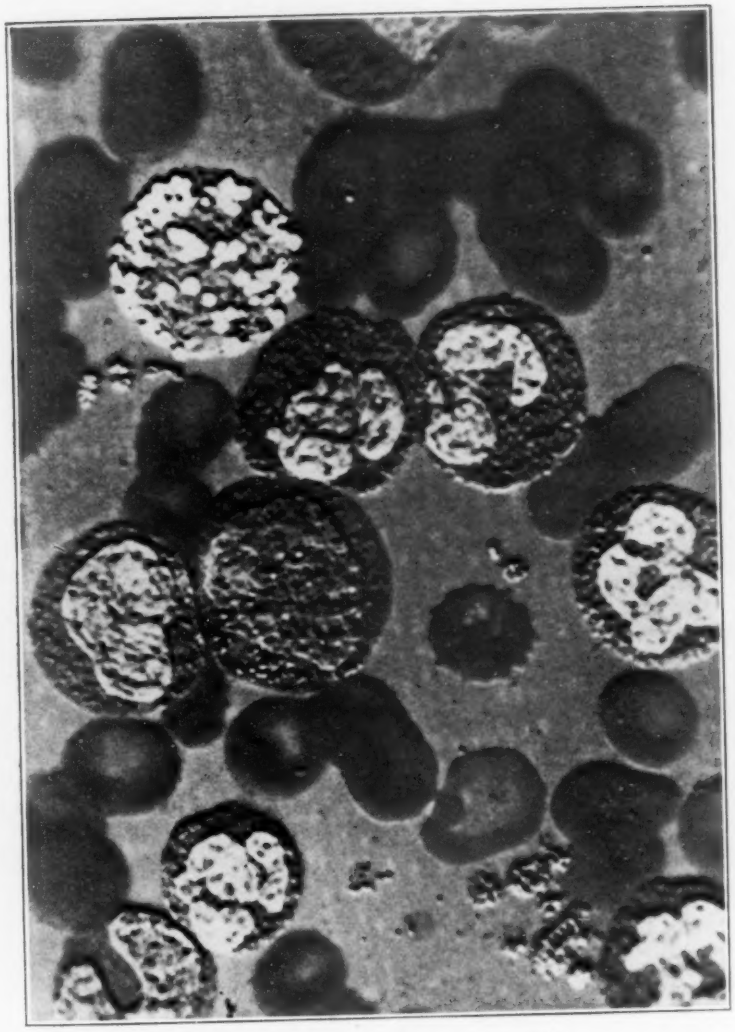

Fig. 11.—Profile of myelogenous leukemia.

Figure 7 shows an interesting but not particularly important profile photomicrograph of the erythrocytes of a Negro boy with sickle cell anemia.

Figures 8 and 9 contrast a usual photomicrograph of blood taken from a patient with chronic lymphogenous leukemia and a profile one of the same blood. It is interesting to note how the nuclei appear to be raised above the level of the cytoplasm, which has undoubtedly contracted over them in the dried, stained smear.

Perhaps the most striking if not the most important contrast between the two methods of printing is shown in figures 10 and 11. The beautiful design in the cells of the myeloid series, particularly in a basophil, in blood from a patient with chronic myelogenous leukemia is a most interesting example of the possibilities in the use of the profile photomicrograph for purposes of illustration and demonstration in hematology.

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SIGNIFICANCE OF GLYCOSURIA

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Nearly three centuries ago Thomas Willis observed the urine from a diabetic patient to be "wonderfully sweet, as if imbued with honey or sugar." Ever since then glycosuria has been of paramount interest to the clinician, for it has become synonymous with diabetes mellitus. However, glycosuria may be due to factors that have no relation to diabetes (e. g., "renal glycosuria"), while, conversely, diabetes may exist in the aglycosuric patient (e. g., in the presence of severe nephrosclerosis). Furthermore, there is a possibility that glycosuria alone is not an index of the severity of diabetes. Hence, controversies exist in the literature concerning the significance of transient glycosuria, the significance of glycosuria associated with a normal blood sugar level and the relative importance of the blood sugar level as compared with the amount of sugar excreted in the urine.

Recent studies in renal physiology have provided information that should clarify some of the misconceptions concerning the presence of dextrose in the urine. This information resulted from the elaboration of Cushny's filtration-reabsorption theory of renal function and the application of newer principles to the problem of the excretion of dextrose. Thus it is now known that the renal glomeruli filter the crystalloids of the blood into the tubules, where they are either reabsorbed or concentrated and subsequently excreted. Accordingly, it is obvious that the excretion of dextrose must be dependent on three factors: (*a*) the concentration of this substance in the arterial blood supply of the glomeruli, (*b*) the rate at which the glomeruli filter it out of the blood and (*c*) the rate at which dextrose filtered out is reabsorbed by the tubules. Hence, before evaluating the significance of glycosuria in any case, it is imperative to consider these three factors.

RENAL FACTORS

Arterial Blood Sugar.—The factors that influence the arterial blood sugar and hence the capillary blood sugar are fairly well recognized. Any phenomenon which causes a disturbance in the absorption of carbohydrates from the intestine, in their storage or in their utilization may influence the concentration of blood sugar. Transient hyperglycemia may occur when carbohydrates are absorbed from the intestinal tract at an increased rate (e. g., in hyperthyroidism [1]) or when there is a relative decrease in the rate of storage of carbohydrates in the liver (e. g., in infections, hepatic damage or emotional excitement). Permanent hyperglycemia may occur in any condition in which there is a permanent excessive rate of glycogen breakdown in the liver or an insufficient rate of formation of hepatic glycogen (e. g., in insulin insufficiency or in toxemia).

Glomerular Filtration.—The glomerular filtrate is essentially the same as blood plasma in that it contains the various crystalloids of the blood in the same

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1. Althausen, T. L., and Stockholm, M.: Influence of the Thyroid Gland on Absorption in the Digestive Tract, Am. J. Physiol. **123**:577, 1938.

concentrations as in the plasma. Thus, 100 cc of glomerular filtrate contains the same amount of dextrose as 100 cc. of blood plasma. Therefore, the amount of sugar that enters the tubules is dependent on the ability of the glomeruli to filter this sugar from the blood. This ability is expressed as the "glomerular filtration rate." On the other hand, the amount of blood plasma which is entirely freed of dextrose in a given time is known as the "dextrose clearance." This represents the amount of sugar which has been filtered out by the glomeruli less that which has been reabsorbed by the tubules (fig. 1). Obviously, in the aglycosuric person the dextrose clearance is zero. Hence, to measure the amount of dextrose which has passed through the glomeruli, it becomes necessary to measure the glomerular filtration rate, i. e., the rate at which the kidneys free the blood plasma of a substance which is neither reabsorbed nor secreted by the tubules. Inulin is such a substance, and the amount of blood which is entirely freed of inulin per minute is known as the "inulin clearance." Since all the inulin which has been filtered

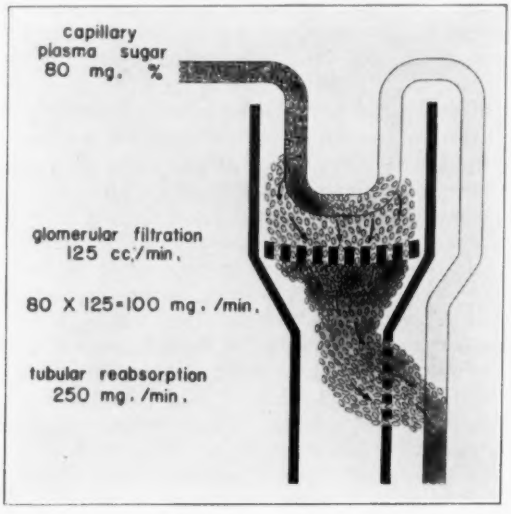

Fig. 1.—Normal. The reabsorptive capacity of the tubules exceeds the dextrose filtration rate (plasma sugar × filtration rate).

into the tubules subsequently appears in the urine, the inulin clearance actually represents the rate of glomerular filtration not only of inulin but of any other solute present in the blood plasma. By such means it has been shown that about 125 cc. of blood is normally freed of its crystalloids per minute. Any disturbance in the functional integrity of the glomeruli (e. g., glomerulonephritis or nephrosclerosis) will impair the filtration capacity and thereby reduce the amount of any solute (inulin, dextrose, urea) that normally can enter the tubules in a unit of time.[2]

2. The clearance of any substance is expressed by the term UV/P, in which U and P represent the concentration of the substance in the urine and plasma, respectively, and V, the volume of urine excreted in a unit of time. For inulin UV/P = 125 cc. per minute. A substance like urea, which partially diffuses back into the blood stream, or a substance like dextrose, which is reabsorbed by the tubules (fig. 1), will have a lower over-all clearance. Since the relation between the inulin clearance and the urea clearance is fairly constant

The amount of dextrose that has been removed from the plasma per minute is represented by the product of the glomerular filtration rate (i. e., the inulin clearance or the urea clearance /0.6) and the concentration of dextrose in the plasma. Thus, at an arterial blood plasma sugar level of 80 mg. per hundred cubic centimeters and a filtration rate of 125 cc. of blood per minute, 100 mg. of sugar will enter the tubules per minute (fig. 1); at a blood sugar level of 220 mg. per hundred cubic centimeters, 275 mg. will enter the tubules per minute (fig. 2). However, if the filtration rate drops because of glomerulonephritis, for example, to 50 cc. per minute, then at the aforementioned blood sugar levels, only 40 mg. (fig. 4) and 110 mg. (fig. 5), respectively, will enter the tubules per minute.

Tubular Reabsorption.—The amount of dextrose that is excreted in the urine is dependent on the balance between the amount of dextrose that enters the tubules

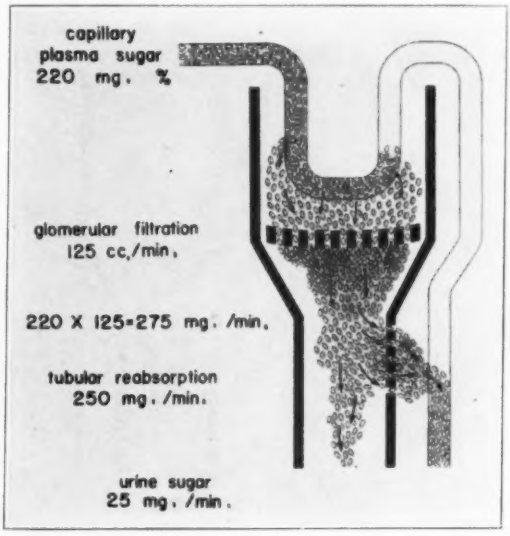

Fig. 2.—Diabetes mellitus. The dextrose filtration rate (plasma sugar × filtration rate) exceeds the maximum reabsorptive capacity of the tubules because the plasma sugar is high.

and the quantity that is transported by the tubules back into the blood stream. The studies of Shannon and Fisher [3] on normal dogs and those of Govaerts and Muller [4]

(inulin clearance = urea clearance /0.6 and parallel each other closely (Smith, H. W.: Note on Interpretation of Clearance Methods in Diseased Kidney, J. Clin. Investigation **20**:631, 1941), one may employ the urea clearance to measure the rate of glomerular filtration (table) instead of using the more difficult inulin clearance procedure. Thus, if a patient has glycosuria, he is made to void at a specific hour, and a sample of blood is taken at the same time. After a definite interval he is made to void and another sample of blood is taken. The volume of urine passed during the interval is noted. Using the average value of the two blood samples, the volume of urine excreted per minute and the values for sugar and urea nitrogen in the urine, the formula UV/P is employed to determine both the urea and the dextrose clearance. Urea clearance /0.6 gives the glomerular filtration rate.

3. Shannon, J. A., and Fisher, S.: Renal Tubular Reabsorption of Glucose in Normal Dog, Am. J. Physiol. **122**:765, 1938.

4. Govaerts, P., and Muller, P.: Mechanism of Glucose Excretion by Kidney in Diabetic Dogs, J. Clin. Investigation **18**:25, 1939.

on diabetic dogs led to the concept that the transfer of dextrose from the tubular urine to the blood (i. e., reabsorption) is accomplished by a mechanism which in its rate of transfer is independent of differences in concentration of sugar in the blood and the tubular urine. It is independent also of the rate of movement of either the tubular urine or the tubular blood supply, i. e., of glomerular filtration or of renal blood flow. The rate of the reabsorption of dextrose then becomes dependent on just two factors: (1) the availability of dextrose in the tubules and (2) the maximum capacity of the tubules to reabsorb dextrose.

As data have accumulated, the maximum reabsorptive capacity has been found to have a reasonably constant value during normal renal function.[5] This value is determined by measuring the amount of dextrose that enters the tubules (glomerular filtration rate × plasma sugar concentration) less the amount which appears in the urine in the same interval of time. This estimation can be used as an index

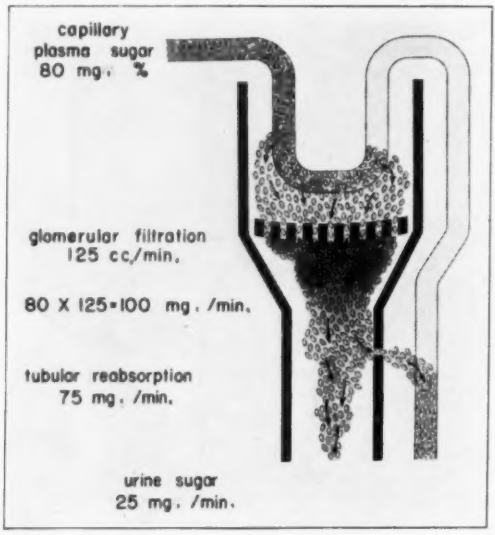

Fig. 3.—"Renal glycosuria." The dextrose filtration rate (plasma sugar × filtration rate) exceeds the maximum reabsorptive capacity of the tubules because of some physiologic, pharmacologic or pathologic deficiency of tubular function.

of the efficiency of one aspect of renal activity just as the glomerular clearance is used of another. In normal man the maximum reabsorptive capacity of the tubules has been found to vary from 250 to 350 mg. per minute.[6] When tubular function is impaired, the reabsorptive capacity of the tubules may be so reduced that dextrose will appear in the urine even at normal or low blood sugar levels (fig. 3).

5. Shannon, J. A.: Kidney, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1942, vol. 4, p. 297.

6. Nelson, N., and Mirsky, I. A.: The Influence of Glomerular Filtration on the Glucose "Threshold" in Man, Am. J. Physiol. **129**:P429, 1940. Steinitz, K.: Studies on Conditions of Glucose Excretion in Man, J. Clin. Investigation **19**:299, 1940. Smith, H. W.; Ranger, H. A.; Chasis, H., and Goldring, W.: The Dispersion of Glomerular Activity in the Normal and Hypertensive Kidney, Am. J. Physiol. **133**:P450, 1941.

RENAL THRESHOLD FOR DEXTROSE

It is apparent from the statements under "Tubular Reabsorption" that while the maximum reabsorptive capacity of the tubule is a basically independent function of the kidney, the threshold for the excretion of dextrose as it is ordinarily understood is not, but is dependent both on the maximum reabsorptive ability of the tubules and on the glomerular filtration rate. For example, with a given ability to reabsorb dextrose, loss of dextrose into the urine will occur whenever it is presented to the tubules more rapidly than it can be handled. Under normal conditions this does not occur because the amount of dextrose filtered out does not approach the maximum reabsorptive capacity of the tubules (fig. 1). However, flooding of the tubules with dextrose may be produced in two ways: 1. A normal rate of glomerular filtration associated with a high concentration of dextrose in the filtrate (high blood sugar) will produce excretion of sugar (fig. 2). 2. If the rate of glomerular filtration is abnormally high, loss of dextrose into the

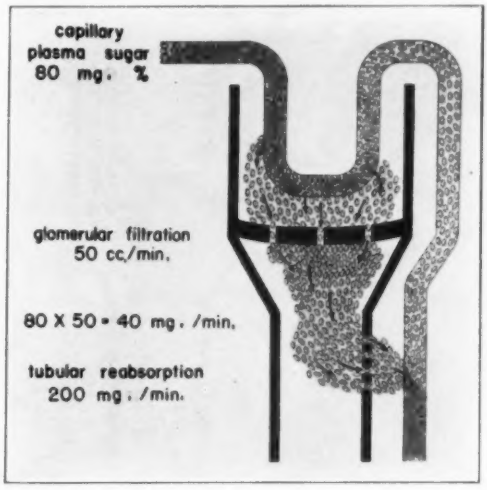

Fig. 4.—Glomerulonephritis. The reabsorptive capacity of the tubules exceeds the dextrose filtration rate (plasma sugar × filtration rate) because of inadequate filtration through the abnormal glomerulus. The blood is not completely freed of dextrose at any time.

urine will occur at a normal or a low concentration of dextrose in the glomerular filtrate. Obviously the latter situation must be extremely rare, but the possibility of it may be revealed by future studies.

Conversely, excretion of sugar in the urine may occur at a normal concentration of dextrose if the reabsorptive capacity of the kidneys is abnormally low. This is the situation encountered in "renal glycosuria" (fig. 3). Here the glomerular function is generally normal while the tubular ability to reabsorb dextrose is so impaired that glycosuria occurs at normal or only slightly elevated blood sugar concentrations.

The renal threshold for dextrose in man in the past has been determined by ascertaining the blood sugar level at which sugar appeared in the urine; the value obtained varied with whether the blood sugar was rising or falling. This procedure does not give a quantitative description of the actual physiologic mechanisms that are involved. Actually the renal threshold for sugar may be defined

as that concentration of blood sugar at which the quantity entering the tubules per unit of time exceeds that which the tubules can reabsorb in the same interval of time. By measuring the rate of glomerular filtration of sugar and the rate at which sugar appears in the urine it is possible to evaluate the transfer of dextrose in the kidney and to assess its efficiency. Quantitatively, the threshold may be expressed by the value for "dextrose reabsorbed per hundred cubic centimeters of glomerular filtrate" (i. e., dextrose reabsorbed/glomerular filtration rate).

It is evident that, given a patient with glycosuria, the glomerular filtration rate will provide information concerning the amount of dextrose that entered the tubules whereas the dextrose clearance [1] will make possible the estimation of the amount of sugar reabsorbed, since the amount of dextrose filtered into the tubules less the amount of dextrose excreted equals the amount reabsorbed. In this manner it becomes possible to evaluate the significance of glycosuria in any case irrespective of the blood sugar level as well as of the status of renal function.

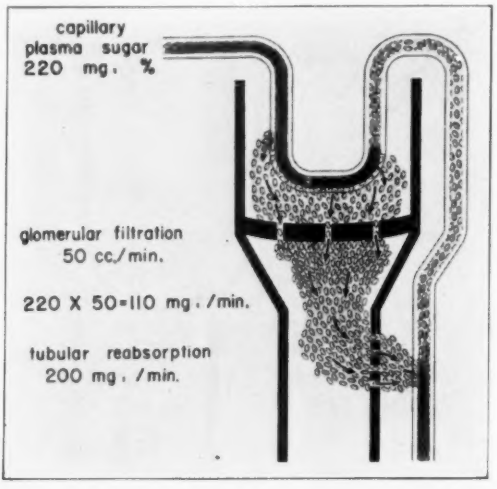

Fig. 5.—Diabetes and nephrosclerosis. The reabsorptive capacity of the tubules exceeds the dextrose filtration rate (plasma sugar × filtration rate) because of inadequate filtration through the abnormal glomerulus.

Renal Glycosuria.—This apparently benign abnormality in the renal control of dextrose excretion has been basically a well understood condition. However, the vagueness of the diagnostic criteria and the confusion of the condition with diabetes mellitus have unnecessarily complicated the detection and subsequently the handling of renal glycosuria. It is obvious that the term "renal glycosuria" should be reserved for those cases in which the excretion of dextrose in the urine is occasioned by an inefficient renal reabsorptive mechanism (fig. 3). It is probable that this inefficiency results from a number of etiologic factors and should, therefore, be distinguished on the basis of these factors as physiologic, pathologic or pharmacologic in nature. Moreover, there is no reason why this same inefficiency in reabsorption of dextrose cannot be accompanied by other causes of glycosuria, such as the hyperglycemia of diabetes mellitus. That does not mean that there is any relation between them other than the fact that diabetes can occur in persons with normal or abnormal kidneys. In other words, the incidence of diabetes mel-

litus in patients with a history of "renal glycosuria" should be the same as it is in the general population.

This view is completely borne out by our data on 3 patients with renal glycosuria (R. T., W. W. and F. W.), who show normal glomerular function but marked reduction in dextrose reabsorbed (table). This reduction is of about the same order of magnitude in each patient; the maximum reabsorptive capacity of the tubules ranges from 75 to 97 mg. per minute, in contrast to the normal ranges of from 250 to 350 mg. per minute. The threshold (dextrose reabsorbed per hundred cubic centimeters of glomerular filtrate) is in each case definitely below the normal fasting sugar level.

Whereas it is possible to find persons suffering from renal glycosuria who may have metabolic disturbances as a result of the constant loss of sugar (i. e.,

Decreased Tubular Reabsorptive Ability in "Renal Glycosuria" and in Bright's Disease

		Clearance		Dextrose				
Patient	Period	Urea Clearance (1)	Urea Clearance/0.6 (2)	Blood, Mg. per 100 Cc. (3)	Filtered Out of Blood (3) × (2), Mg. per Min. (4)	Excreted, Mg. per Min. (5)	Reabsorbed (4) − (5), Mg. per Min. (6)	Threshold (6) / (2), Mg. Reabsorbed per 100 Cc. of Glomerular Filtrate (7)
R. T.	1	..	115*	82	95	19	75	65
	2	..	114	81	92	16	76	67
	3	..	115	80	92	15	77	67
	Average	..	115	81	93	17	76	66
F. W.	1	..	123	90	111	12	99	80
	2	..	112	88	99	9	90	80
	Average	..	118	..	..	..	95	80
W. W.	1	66	110	80	88	11	77	70
	2	57	95	81	77	10	67	71
	Average	..	...	..	..	..	72	71
M. E.	1	25	41	325	133	16	117	285
	2	25	42	307	129	15	114	271
	3	21	34	306	103	12	91	268
	4	19	32	303	97	10	87	272
	Average	..	..	...	..	..	103	276
L. T.	1	37	61	258	157	54	103	169
	2	41	67	226	151	43	108	161
	3	36	60	224	134	36	98	163
	Average	..	..	...	...	..	104	165

* Inulin clearance; simultaneous urea clearance.

relative starvation), there is no evidence of such difficulties in the 3 whose cases have been cited. There has been no evidence of starvation or ketosis in these cases, nor could any be anticipated from the magnitude of the loss of sugar occurring if a normally adequate dietary regimen was permitted. In these 3 persons with impaired tubular reabsorptive ability for dextrose no evidence of additional renal dysfunction was found, nor was there any history suggestive of a responsible factor in the origin of this condition. This situation is that encountered in the patient with true or idiopathic renal glycosuria.

A similar situation can be produced experimentally by the administration of phlorhizin, which inhibits the reabsorption of dextrose, presumably by inhibiting phosphorylation in the tubules,[7] and therefore the condition produced may be

7. Rapoport, S.; Nelson, N.; Guest, G. M., and Mirsky, I. A.: The Turnover of Acid-Soluble Phosphorus in the Kidneys of Rats, Science **93**:88, 1941.

regarded as a pharmacologic type of renal glycosuria. Here, too, no metabolic disturbance ensues so long as the patient eats an adequate amount of carbohydrate and thereby compensates for the loss in the urine.

"Bright's Disease."—In patients with various renal diseases one finds lowered tubular capacity to reabsorb dextrose similar in severity to that in patients with renal glycosuria. As data accumulate, it is probable that instances will be encountered in which a disease process of known genesis more or less specifically involves this tubular mechanism. Such cases would show continuous glycosuria of the same type as that found in cases of renal glycosuria. However, in each case of pathologically low tubular reabsorptive capacity which we have studied so far, we have found glomerular dysfunction of sufficient magnitude to raise the threshold for sugar spillage to normal or nearly normal levels (fig. 6).

Two examples of patients with Bright's disease (M. E. and L. T.) with this parallel injury to the tubules and the glomeruli are given in the table. It is apparent

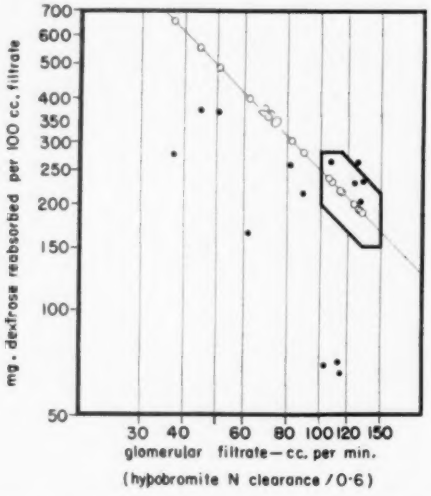

Fig. 6.—Glomerular filtration and renal threshold. The influence of glomerular filtration on the renal threshold for dextrose. The open circles indicate the theoretic reabsorptive capacity of the normal kidney. The black circles indicate the actual data obtained in various patients, showing that if the glomerular filtration is decreased there is also a tendency for the tubular reabsorption to decrease. When the latter does not decrease as much as the former, the threshold for dextrose is increased.

that neither of these persons would normally be apt to have glycosuria (fig. 4). However, should the pathologic disturbance involve the tubules to a greater degree than the glomeruli, glycosuria would ensue. This has been observed occasionally in Bright's disease, in consequence of which the status of the patient's carbohydrate metabolism was questioned.[8] On the other hand, should the pathologic process involve the glomeruli of a patient with diabetes to a greater degree than it involves the renal tubules, glycosuria would decrease since less sugar would be filtered into the tubules (fig. 5). It cannot be emphasized too often that a disturbance in renal

8. Williams, J. R., and Humphreys, E. M.: Clinical Significance of Blood Sugar in Nephritis and Other Diseases, Arch. Int. Med. **23**:537 (May) 1919.

function and the consequent production of glycosuria does not necessarily have any metabolic significance if the loss of calories is adequately compensated.

It is a common observation that the elderly patient with diabetes shows a "decreased renal threshold" in that a high blood sugar level may be encountered without as great glycosuria as might be observed in a younger patient with diabetes. In fact, such elderly patients may be aglycosuric in spite of a high blood sugar level. This has led to much speculation concerning the severity of the diabetic syndrome in the elderly patient, the contention being that the lesser glycosuria indicates a milder disease. However, analysis by means of the procedures described in the preceding paragraphs reveals that the decreased glycosuria is due either to a decrease in glomerular filtration, consequent to pathologic changes in the glomeruli (fig. 5), or to an increase in capacity to reabsorb dextrose, i. e., to a disturbance in renal function and not to some extrarenal metabolic factor. That the elderly diabetic person need not have a different threshold in comparison with the young diabetic person may be illustrated by the observation that a patient 14 years of age with a diabetic history of several years' duration had a renal threshold of 254 mg. per hundred cubic centimeters, while another patient aged 60 years had a threshold of 257 mg., yet the child showed a much more severe clinical picture than did the elderly patient. The only conclusion that can be drawn from this illustration is that the kidneys function equally well in both but that the general metabolic disturbance is greater in the child. Hence, when the glycosuria is diminished in an elderly subject, it may merely reflect some pathologic change in the kidney.

SUMMARY

It is apparent that glycosuria reflects not only the metabolic phenomena which produce hyperglycemia but the physiologic status of various functional units of the kidney. Hence a proper appraisal of the significance of glycosuria necessitates determination of the rates of glomerular filtration and tubular reabsorption as well as of the concentration of blood sugar. In the normal person all three factors are normal (fig. 1). In the patient with "renal glycosuria" or glycosuria induced with phlorhizin and probably in the patient with glycosuria of pregnancy the reabsorptive capacity is decreased (fig. 3). In the patient with diabetes mellitus the blood sugar is high and the renal factors are normal (fig. 2). In the aged person with diabetes and nephrosclerosis there may be a greater or lesser impairment of the functional units of the kidneys, which results in a decrease in the glomerular filtration rate and hence in an increase in the concentration of blood sugar required to produce glycosuria (figs. 5 and 6).

Accordingly, the concentration of sugar in the urine, in itself, is not an index of the severity of the metabolic disturbance that may be present nor does it give any information concerning the prognosis. Only when the renal factors are properly evaluated does the amount of dextrose in the urine become significant. Then one can determine the amount of carbohydrate which the patient retains on a specific dietary intake and thereby arrive at a proper evaluation of the severity of the metabolic disorder.

The May Institute for Medical Research.

ENCEPHALOPATHY FOLLOWING MAPHARSEN THERAPY

PATHOLOGIC REPORT WITH UNUSUAL FINDINGS

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Although mapharsen has been widely adopted in the treatment of syphilis since 1934, reports of fatalities from toxic effects following its use are few. In 1933 Cole and others [1] reported the first case of death attributed to mapharsen; acute nephrosis was the primary cause of death. Two years later Simon and Iglauer [2] reported a case in which a patient had died of anuria after five injections of mapharsen. Shortly afterward Rein and Wise [3] added 2 more cases with fatal outcome. In 1 of these aplastic anemia had developed; in the other granulocytopenia. In 1941 Kirkham and Perlmutter [4] reported a case in which death was due to aplastic anemia following twenty injections of mapharsen.

The first report of mapharsen therapy followed by involvement of the central nervous system appeared in 1939 from India. Rajam and Rao [5] described a case in which hemorrhagic encephalitis followed the use of mapharsen. This complication occurred in a man aged 47 with primary syphilis and a positive serologic reaction for syphilis and followed the second injection of 0.04 Gm. of mapharsen. The first injection had been given five days previously. Within twenty-four hours confusion, generalized rigidity, exaggerated tendon reflexes and extensor plantar responses developed. Death supervened in twenty-four hours. On gross examination "a full and engorged condition of the vessels of the surface of the brain" was noted. Results of microscopic examination were not reported.

A second case was recorded by Chargin [6] in 1940. A patient had received 1.2 Gm. of mapharsen intravenously in five days by the continuous intravenous drip method. Two days after the completion of treatment, convulsive seizures developed and the patient lapsed into stupor. He responded to therapy and recovered in five days. The case presented here is the first in which histopathologic study of the brain was made.

Presented at a meeting of the Brooklyn Neurological Society, Nov. 25, 1941.

From the Neurologic Service and the Neuropathology Laboratory (Department of Pathology, Dr. William W. Hala, director), Kings County Hospital.

1. Cole, H. N., and others: Coöperative Clinical Studies in Treatment of Syphilis: Arsenical Reactions, Ven. Dis. Inform. **14**:173, 1933.

2. Simon, S. D., and Iglauer, A.: Death Following Mapharsen Therapy, Am. J. Syph., Gonor. & Ven. Dis. **23**:612, 1939.

3. Rein, C. R., and Wise, F.: Mapharsen in the Treatment of Syphilis in Office Practice, J. A. M. A. **113**:1946 (Nov. 25) 1939.

4. Kirkham, D., and Perlmutter, M.: Fatal Aplastic Anemia Following Use of Mapharsen: Report of Case, Arch. Dermat. & Syph. **43**:111 (Jan.) 1941.

5. Rajam, R. V., and Rao, N. V.: Mapharside in the Treatment of Syphilis: Clinical Study, Indian M. Gaz. **74**:24, 1939.

6. Chargin, L.: Massive Arsenotherapy in Early Syphilis by Continuous Intravenous Drip Method: Toxicologic Manifestations, Arch. Dermat. & Syph. **42**:248 (Aug.) 1940.

REPORT OF A CASE

History.—A 27 year old man was referred to the outpatient department of the Kings County Hospital in February 1939 by his private physician after he was found to have a positive Wassermann reaction. The patient attended the clinic regularly, was not granted any rest periods and by Feb. 15, 1941 had received forty-nine injections of a bismuth compound and forty-four injections of mapharsen. On February 17 he fell and fractured his left femur. He was unable to return to the clinic until April 5, when 0.04 Gm. of mapharsen was administered intravenously at 10 a. m. Two hours later, while at home, he was found having a generalized convulsion. He was admitted to the neurologic service of Dr. A. M. Rabiner, Kings County Hospital, approximately three and one-half hours after the injection.

On admission the patient was stuporous, had a dusky blue appearance and was breathing irregularly. The chest was clear and resonant. The heart tones were poor, and the rhythm was regular. The blood pressure was 80 systolic and 50 diastolic. The abdomen was soft; no organs were felt. There was bilateral pes cavus.

On neurologic examination the right pupil measured 3.5 mm., the left one 2.0 mm. Neither iris reacted to light. The eyes often deviated to the left. There were twitchings of the perioral group of muscles on the left side and chattering movements of the jaw. The deep

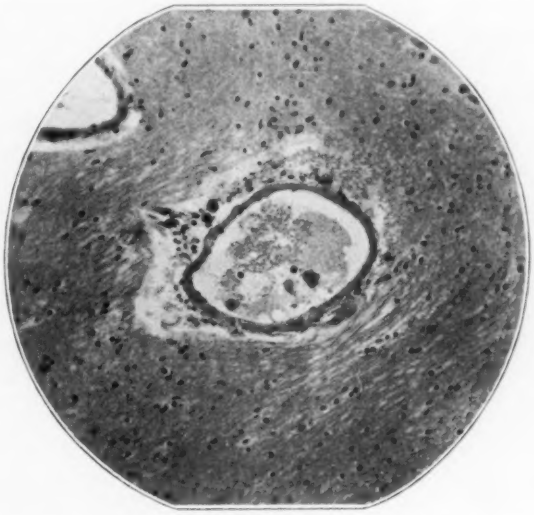

Fig. 1.—Perivascular necrosis. Several phagocytes loaded with hemosiderin can be seen. Hematoxylin and eosin; high magnification.

reflexes were decreased throughout; the superficial ones could not be elicited. There were bilateral Babinski responses of the toes. The patient did not respond to pin prick.

Shortly after admission the patient partially regained consciousness. The following day he could not void, and catheterization was required. Two days later hemiplegia, hemianesthesia and homonymous hemianopia developed, all on the left side.

Each day for twelve days, until April 17, the patient was observed in one or more convulsions. During a convulsion, consciousness was maintained, the head and eyes were turned to the left and there were clonic movements of the entire left side of the body. Occasionally, such movements were noted on the right side.

On April 18, the thirteenth day of hospitalization, the patient lapsed into a stuporous state. Failure to respond to ordinary measures and the predominance of unilateral signs suggested a localized lesion. The patient was then transferred to the neurosurgical service of Dr. E. Jefferson Browder. Ventriculographic studies revealed dilatation of both lateral ventricles and anomalous formation of the corpus callosum.

The patient did not regain consciousness. On April 22 twitchings of the right side of the mouth were noted. On that day, the patient's temperature rose to 105 F. and death ensued, twenty-one days after admission.

Laboratory Data.—Repeated lumbar punctures yielded clear fluid under normal pressure. There was no abnormal cytologic response until April 19, the day after the patient lapsed into stupor, when examination of spinal fluid revealed 74 mononuclear cells per cubic millimeter. The Wassermann reaction of the blood and of the spinal fluid was 4 plus. Results of chemical examination of the blood and urinalysis were within normal limits. A blood count revealed mild leukocytosis.

Autopsy.—General Examination: Gross examination. Significant changes were encountered in the lungs and the liver. Confluent areas of bronchopneumonia were scattered throughout the pulmonary fields. The liver weighed 1,000 Gm. and exhibited a mild degree of fatty metamorphosis.

Histologic examination. Marked active congestion and many areas of acute bronchopneumonia were seen in the lung. The hepatic tissue was moderately swollen and congested. There were a few focal collections of round cells around the bile ducts and a slight increase in fibrous tissue in the periportal areas.

Examination of the Brain: Gross examination. Scattered small and discrete areas of bleeding into the subarachnoid space were revealed. The arachnoid was cloudy, thickened and edematous over the superior convexities and at the base. The vessels of the pia exhibited

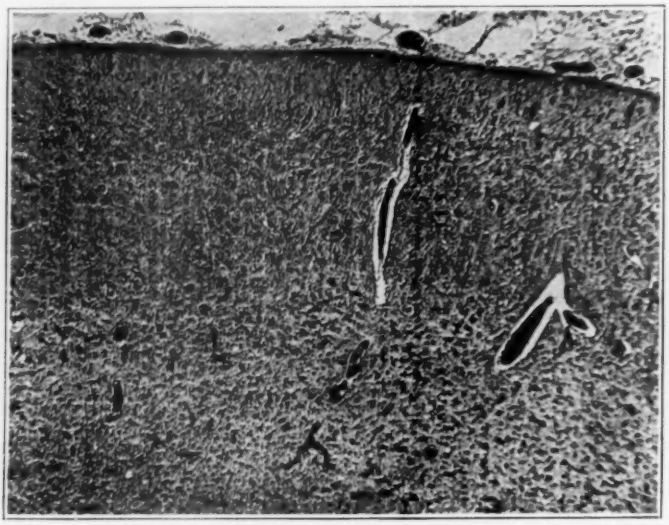

Fig. 2.—Diffuse degeneration seen in deeper layers of the cortex. Mallory's phosphotungstic acid–hematoxylin stain; medium magnification.

considerable congestion. The corpus callosum was poorly developed and was represented by only a thin strand of tissue half an inch (1.25 cm.) in length in the region of the genu. The septum pellucidum was absent, and the columns of the fornix were rudimentary. The white matter was moderately congested. A small group of petechial hemorrhages, apparently related to the ventricular puncture, were seen in the white matter of the left parieto-occipital region. In the white matter of the left frontal operculum a small orange cyst was encountered. There was bilateral dilatation of the ventricular system, most marked in the right temporal horn.

Histologic examination. Sections from various parts of the brain were stained with hematoxylin and eosin, with Mallory's phosphotungstic acid–hematoxylin stain and by the methods of Spielmeyer, Mahan, Fincher and Cajal.

Edema was widespread but generally focal and most marked in the cerebral cortex. Considerable congestion and stasis were present in the small vessels and capillaries of the cortex, in the periventricular gray matter and, to a lesser extent, in the white matter. The stasis was often associated with the presence of a small number of red blood cells in the peri-

vascular spaces. Petechial hemorrhages were seen in scattered parts of the brain, principally in the gray matter. Small and medium-sized arteries in the cortex, white matter and basal ganglions were surrounded by rarefied zones of necrosis. The rarefied zones contained macrophages distended with hemosiderin. They appeared to be the remains of previous minute perivascular hemorrhages.

Two types of degenerative lesions formed a distinctive part of the pathologic condition. The first was evident in the temporal lobe, where poorly circumscribed areas of degeneration involved the deepest layers of the cortex and extended parallel to the surface in a laminar fashion (fig. 1). At times all cortical layers were included in the degenerative process. This pathologic process stopped sharply at the edge of the white matter. These lesions had a chaotic and disorganized aspect (fig. 2). In them the ground substance was spongy, edematous and disintegrating. The normal layers of the cortex could not be made out. The ganglion cells had disappeared. There was considerable gliosis, the tissue consisting chiefly of plump, protoplasmic astrocytes. The blood vessels appeared normal.

A second type of degenerative lesion also occurred in the cortex but was smaller, more discrete and more localized (fig. 3). Within these lesions ganglion cells and glia were absent. Nests of closely aggregated capillaries formed by the proliferation and dilatation of small

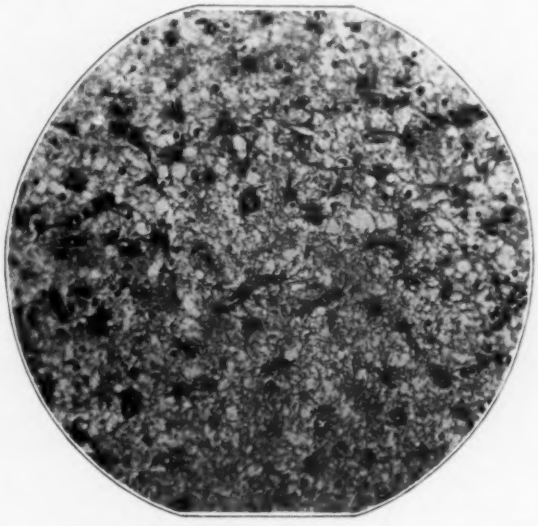

Fig. 3.—Higher magnification of the degeneration seen in figure 2. Note the spongy state of the tissue and the numerous astrocytes. Mallory's phosphotungstic acid-hematoxylin stain.

vessels constituted a striking feature of this lesion. This was well seen in sections stained with silver stain (fig. 4), which demonstrated increase in perivascular connective tissue. Scattered through one such focus in the frontal lobe were several small petechial hemorrhages which had ruptured into the subarachnoid space. The arachnoid overlying this area was hyperplastic and infiltrated with red blood cells.

The ganglion cells appeared normal except in the foci of degeneration. Considerable gliosis of protoplasmic type was present throughout the cortex but was most marked in the temporal lobe. This gliosis was seen even in areas which had not undergone degeneration. A few small, spongy, demyelinated foci, bearing no relation to blood vessels, were encountered here and there in the white matter. In some areas the arachnoid was infiltrated to a slight degree with a small number of lymphocytes and plasma cells. Occasionally, the wall of a medium-sized vessel in the cortex was similarly infiltrated. The vessels, however, did not exhibit either thickening or thrombosis. The macroscopic cyst in the opercular region was surrounded by a zone of demyelination and gliosis.

Determination of arsenic was carried out on the fixed brain, and 0.005 mg. as arsenous oxide (As_2O_3) per hundred grams was found.

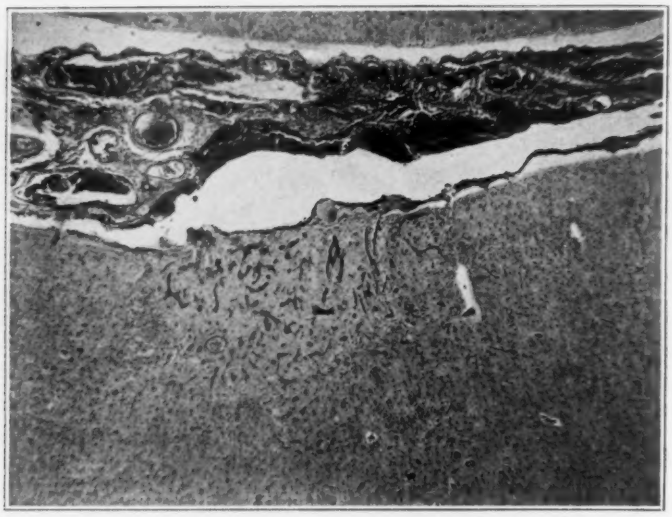

Fig. 4.—Discrete focal necrosis in the cortex. Note the vascular proliferation and the disappearance of cells in the lesion. Hemorrhagic exudate is evident in the subarachnoid space. Nissl's stain; low magnification.

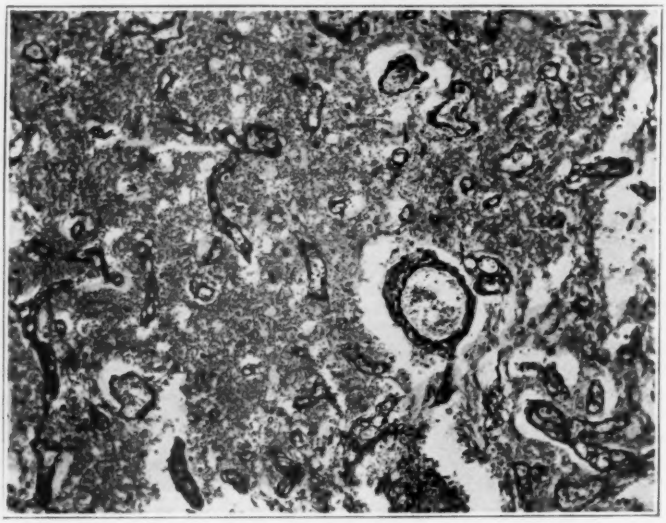

Fig. 5.—Higher magnification of the lesion seen in figure 4. Note the proliferation of the perviascular reticulum and the formation of new vessels. There is a spongy state of the tissue, and both ganglion cells and glia are absent. Fincher's stain; high magnification.

COMMENT

Cerebral complications following the use of arsphenamine and related drugs are by no means rare. They have been described under various names, viz., hemorrhagic encephalitis, arsenical encephalitis, pericapillary encephalorrhagia, purpura of the brain, etc. Headache, vomiting, convulsions, unconsciousness, cyanosis and collapse, disturbances of the pupillary and extraocular muscles, loss of control of sphincters, mental disturbances and various types of paralysis are characteristic of the disorder. The symptoms are those of an acute diffuse cerebral disorder, and the clinical syndrome in this case conforms to that generally seen. In 104 cases of hemorrhagic encephalitis reviewed by Glasser, Imerman and Imerman [7] the symptoms of involvement of the central nervous system generally made their appearance in twelve hours to six days after an intravenous injection of an arsenical. A generalized convulsion marked the beginning of our patient's illness, as is frequently the case, and this occurred two hours after the injection of 0.04 Gm. of mapharsen. The absence of changes in the spinal fluid in this case conforms to the experience of other authors.

There were, however, unusual clinical features in this case. Until now, in only 1 reported case have cerebral complications and fatal outcome been attributed to mapharsen. In Glasser's series any fatal cerebral complications always occurred before the fifteenth injection of an arsenical, 78 per cent of the complications occurring after one of the first three doses. Our patient had received forty-five injections of mapharsen. There was, however, an interval of six weeks between the forty-fourth and the forty-fifth injection. During that time a fracture of the femur had prevented the patient from attending clinic for treatment. In Glaser's analysis of 69 cases in which the survival period was stated, death occurred within eight days after the development of symptoms in all cases but 1. Our patient survived for twenty-one days.

The pathologic characteristics of arsphenamine encephalopathy have received considerable attention. The principal feature has been described as petechial hemorrhages, which often take a ring form. The hemorrhages generally were situated about small blood vessels and have been said to occur chiefly in the white matter. This hemorrhagic feature has been emphasized by most authors, but it is not the only form of pathologic change to be found. Earlier reports by Busse and Merian,[8] Schmorl [9] and Stühmer [10] called attention to necrotic lesions in the brain in association with petechial hemorrhages or in their absence. Russell [11] reported 3 cases "in which administration of arsphenamine was followed by the production in the central nervous system not only of perivascular and ring hemorrhages, but also of perivascular non-hemorrhagic areas of necrosis and demyelination."

Roseman and Aring [12] have also reported a degenerative type of lesion in a case in which the complication developed after the fifteenth injection of neoarsphenamine. They stated: "The most important lesions in the brain were focal perivascular areas of necrosis unrelated to hemorrhage in the white matter." The

7. Glaser, M. A.; Imerman, C. P., and Imerman, S. W.: So-Called Hemorrhagic Encephalitis and Myelitis Secondary to Intravenous Arsphenamines, Am. J. M. Sc. **189**:64, 1935.

8. Busse, O., and Merian, L.: Ein Todesfall nach Neosalvarsaninfusion, München. med. Wchnschr. **59**:2330, 1912.

9. Schmorl, G.: Encephalitis Hemorrhagica nach Salvarsaninjektionem, München. med. Wchnschr. **60**:1685, 1913.

10. Stühmer, A.: Hirnschwellung nach Salvarsan, München. med. Wchnschr. **66**:96, 1919.

11. Russell, D.: Changes in the Central Nervous System Following Arsphenamine Medication, J. Path. & Bact. **45**:357, 1937.

12. Roseman, E., and Aring, C. D.: Encephalopathy Following Neoarsphenamine Therapy, New England J. Med. **224**:550, 1941.

perivascular necrosis was related to changes in the small blood vessels, chiefly in the endothelium, which frequently occluded the vessel. Petechial hemorrhages did not seem to be important.

Pollak and Riehl [13] reported 2 cases of arsphenamine encephalopathy, in the first of which there was edema but no hemorrhages and microscopically revealed moderate degenerative changes in the ganglion cells and severe disease of the glia. They encountered increase in glia in the deepest layers of the cortex, many of which were undergoing severe degeneration. One small area of necrosis was encountered in the pulvinar. The severe glial reaction in the cortex was similar to the marked cortical gliosis encountered in our case.

The pathologic alterations in the case reported here consisted of stasis, edema, petechial bleeding, degeneration and gliosis. An occasional ring hemorrhage was encountered. The fresh recent bleeding took place predominantly in the gray matter of the cortex, principally in the parieto-occipital region, and seemed to be related to the ventricular puncture. Older, more widespread perivascular petechial hemorrhages were represented by small necrotic, cribrose, perivascular foci containing small numbers of phagocytes loaded with hemosiderin. The macroscopic orange cyst in the white matter of the frontal operculum represented a hemorrhagic scar of this type. This cyst was surrounded by a zone of demyelination containing numbers of astrocytes. A similar lesion was described by Globus and Ginsburg.[14]

Lesions of a necrotic type, generally small and confined to the gray matter, were a prominent part of the pathologic change in this case. One aspect of this necrotic-degenerative feature was characterized by small focal acellular areas in which there was proliferation of vessels and of perivascular connective tissue without gliosis. A second type of necrotic-degenerative lesion was more diffuse and confined to the cortex. The latter type is of special interest and calls for comment. This lesion extended for some distance in the gray matter of the cortex in a laminar fashion. The deeper layers were more severely involved, and the pathologic changes consisted of marked increase in astrocytes, a spongy state of the ground substance and total disappearance of the ganglion cells (see fig. 3). In the same region the more superficial layers demonstrated considerable increase in astrocytes, but the spongy state was lacking and the ganglion cells were less severely involved. Here the process seemed of the same type as that encountered deeper in the cortex, though less severe and less advanced. At times the severer phase extended throughout the thickness of the cortex. This type of lesion resembled the pathologic changes encountered by Pollak and Riehl. It seemed as though this process was progressive and continuous and had affected the deeper layers earlier and more severely. This conception of progressive degenerative changes occurring in the wake of a toxic process the acute phase of which had subsided was of a different order from the changes due to the toxin directly, which could be considered as essentially hemorrhagic. This lends support to the view of Baker [15] and Russell [11] that the degenerative features belonged to processes of longer duration and were related to the time factor. The necrotic foci encountered in our case, however, are unlike those described by Russell, inasmuch as hers were simply demyelinating lesions.

The significance of these lesions is not clear. Whether they represent a mapharsen effect is not known. Reactions to mapharsen have been too few, and

13. Pollak, E., and Riehl, G., Jr.: Zur Pathologie der Salvarsanschäden des Nervensystems, Jahrb. f. Psychiat. u. Neurol. **47**:99, 1930.

14. Globus, J. H., and Ginsburg, S. W.: Pericapillary Encephalorrhagia Due to Arsphenamine: So-Called Arsphenamine Encephalitis, Arch. Neurol. & Psychiat. **30**:1226 (Dec.) 1933.

15. Baker, A. B.: Hemorrhagic Encephalitis, Am. J. Path. **11**:185, 1935.

those in the brain have been rare. Pathologic studies have not as yet been reported. It is possible that these necrotic lesions may represent an unusual reaction of the brain to arsenic occurring under special circumstances and related to the time factor and the special conditions of tissue and vessel reactivity obtaining when prolonged administration of the drug is followed by a prolonged interruption in treatment, followed in turn by resumption of treatment.

As far as the hemorrhagic tendency is concerned, most of this was in relation to the ventricular puncture except for occasional small scattered petechial hemorrhages and the frequent small perivascular aggregates of phagocytes containing hemosiderin which indicated prior hemorrhage. Inasmuch as the patient had been well prior to the onset of the present illness, it is presumed that these represented hemorrhages which occurred early in the course of the illness and were therefore part of the response of the brain to arsenic. The necrotic-degenerative lesions and the gliosis were in excess of the hemorrhagic features and dominated the pathologic picture. This is more in keeping with the cases reported by Russell, by Roseman and Aring and by Pollak and Riehl.

In any event, petechial hemorrhages are not the only form of pathologic change encountered in the central nervous system as a complication of arsenical therapy. Indeed, hemorrhages may be in the background or even nonexistent. It would therefore be an error to ascribe the clinical picture to "hemorrhagic encephalitis" or "pericapillary encephalorrhagia." The broader term arsenical encephalopathy is considered more universally appropriate and does not commit one to the expectation of bleeding.

It should also be emphasized that when petechial bleeding occurs in the brain, the cerebrospinal fluid may give no indication of it. A clear spinal fluid should, therefore, not be considered to exclude the presence of petechial hemorrhages in the brain.

Although there was an increase in astrocytes in various regions of the cortex, the ganglion cells were spared except in the necrotic foci and the areas of degeneration. The ganglion cells as such were therefore not affected primarily by the disease. In a few areas the meninges exhibited a small degree of localized infiltration by lymphocytes and plasma cells suggestive of syphilitic meningitis. A few vessels were similarly affected to a slight degree. But nowhere was there any thickening or sclerosis of vessels, thrombosis or occlusion to suggest that syphilis of the vascular system played any role in the genesis of the pathologic changes. In the absence of significant vascular disease the necrotic-degenerative lesions have been interpreted as toxic in origin. In the absence of previous neurologic illness the clinical syndrome was clearly related causally to the mapharsen. In its general features it conformed to the clinical features of reported cases of arsenical encephalopathy. The pathologic changes have therefore been ascribed to mapharsen.

SUMMARY

A case is presented in which fatal cerebral symptoms developed after mapharsen therapy.

The patient had received forty-five injections of the drug, but the last was preceded by an interval of six weeks during which the patient did not receive any medication.

The symptoms were those commonly seen in arsenical encephalopathy.

The pathologic changes in the brain consisted of petechial hemorrhages and necrotic-degenerative lesions of an unusual type.

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POSTANGINAL SEPSIS

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Septicemia may be due to a number of causes. It is important to determine the exact cause in order that proper treatment may be instituted. The purpose of this paper is to call attention to one cause of septicemia often overlooked by the physician, namely, septic phlebitis of the internal jugular vein or of one of its branches.[1] This condition is usually called postanginal sepsis or postanginal pyemia [2] because it almost always follows an infection of the throat. Failure to recognize this dangerous disease has resulted in many fatalities. Early diagnosis and operation may save the life of the patient.

Few reports of cases of postanginal sepsis are found in the American literature, although German and French observers have published many. Two cases are reported here to illustrate the clinical picture and the diagnosis of this entity.

REPORT OF CASES

CASE 1.—D. W., a white girl of 15, was admitted to the Montefiore Hospital April 21, 1938. The past medical history was without import. The illness began on April 17 with stuffiness of the nose and slight soreness of the right side of the throat, the latter lasting about two hours. On the second day the oral temperature was 101 F., the pulse rate 95 and the respiratory rate 18 per minute. Physical examination disclosed only slight prominence and redness of the right tonsil. There was no enlargement of the cervical gland. The ears, the pharynx, the nose and the paranasal sinuses were normal. On the third and fourth day of the illness the patient had fever, slight chilliness and sweating but no sore throat.

On April 21 the oral temperature was 105 F., the pulse rate 130 and the respiratory rate 22 per minute. A slight cough had developed during the past few hours. Physical examination gave completely negative results; the slight redness and prominence of the right tonsil were now absent. The patient was admitted to the hospital with a diagnosis of central pneumonia. Roentgen examination, however, revealed normal lungs. A specimen of urine obtained by catheter revealed no abnormalities. The hemoglobin determination was 75 per cent; the red cells numbered 3,640,000 and the white cells numbered 18,400 per cubic millimeter of blood, with 86 per cent polymorphonuclear cells present.

From April 22 to May 3 the patient was critically ill. For days the oral temperature ranged from 96 to 99 F. in the morning and from 105 to 106.7 F. in the afternoon or evening. On other days the temperature was continuously elevated, 103 to 105 F. The pulse rate varied from 90 to 140 per minute. The patient had frequent severe chills, followed by profuse sweating. The physical examination, including pelvic and neurologic examinations, gave entirely negative results during the first twelve days of hospitalization. The clinical impression was sepsis of unknown origin.

On May 4 examination revealed a new condition, namely, slight swelling of the right side of the neck at the level of the angle of the jaw. This was slightly tender and seemed to lie beneath the sternocleidomastoid muscle. At the same time slight prominence of the right tonsil reappeared, similar to the finding of April 18. The occurrence of these slight abnormalities on the same side as the recent soreness of the throat suggested the possibility of a deep infection of the neck associated with phlebitis of the internal jugular vein to explain the clinical picture of sepsis. Operation on the right side of the neck was advised, but a surgical

1. Mosher, H. P.: Submaxillary Fossa Approach to Deep Pus in the Neck, Tr. Am. Acad. Ophth. **34**:19, 1929.

2. (*a*) Abt, I. A.: Postanginal Sepsis, J. Pediat. **1**:8 (July) 1932. (*b*) Waldapfel, R.: Die postanginöse Pyämie, Ztschr. f. Hals-, Nasen- u. Ohrenh. **23**:178, 1929. (*c*) Burchardt, S.: Ein Beitrag zur Pathogenese der postanginösen Sepsis, ibid. **23**:97, 1929.

consultant saw no indication for surgical intervention since the tonsil and the pharynx were normal in appearance. The tenderness and swelling of the right side of the neck and the slight protrusion of the right tonsil disappeared after three days. The fever and chills continued. The hemoglobin determination dropped to 56 per cent and the erythrocyte count to 2,430,000. The leukocytes ranged from 7,600 to 13,000 per cubic millimeter; the neutrophils varied from 75 to 90 per cent. Five blood cultures were sterile. Agglutination tests for tularemia, typhoid, paratyphoid and undulant fever were negative. The Wassermann and Kahn tests of the blood were negative. The urine was essentially normal. Sulfanilamide was administered to the patient shortly after her admission to the hospital. She received a total of 1,290 grains (83.4 Gm.) in twenty-three days. The drug had no effect on her condition. The only other treatment consisted of nine blood transfusions, averaging 250 cc., and general supportive measures. The oral temperature continued to swing from 99 to 106 F. daily. There were no subjective symptoms other than weakness, anorexia, chills and sweating. General physical examination disclosed only a soft systolic blow at the mitral area. The development of a cardiac murmur suggested the possibility of acute bacterial endocarditis, but the negative blood cultures and the absence of embolic phenomena precluded this diagnosis.

On May 15 slight swelling reappeared at the angle of the right jaw. This was slightly tender and similar to that noted on May 4. Because of these signs and because of the persistence of sepsis, a diagnosis of jugular phlebitis was made despite the negative blood cultures and the normal appearance of the tonsil and the pharynx.

On May 16 Dr. S. Rosenberg exposed the internal jugular vein on the right side. Moderate difficulty was encountered in exposing the carotid sheath, as the latter was infiltrated and adherent to several enlarged, inflamed lymph nodes. The internal jugular vein was discolored and presented a dull white appearance in contrast to the usual blue color. The vein had lost its elasticity and was unaffected by the respiratory excursions. A ligature was placed about the vein in the lower part of the neck, and a small portion was excised. There was no mural thrombus at the site of ligation, but the wall of the vein was definitely thickened. The right tonsil was removed by Dr. S. Ratner. When the tonsil was raised from its bed, about 2 ounces (59 cc.) of pus gushed from the space behind it. In the lateral pharyngeal wall at the level of the tonsil was a large perforation through which pus oozed. It communicated with an abscess cavity which occupied the parapharyngeal space.

The postoperative course was stormy. The oral temperature ranged from 96 to 106 F. for five days. On the sixth day the temperature became normal. During the next two weeks there was no further rise in temperature or recurrence of chills. The cardiac murmur disappeared. After a stay of thirty-eight days in the hospital the patient was discharged completely recovered. At the time of writing she has remained well for four years.

The pus obtained from the abscess yielded a growth of staphylococci on culture. The pathologic findings were (1) retrotonsillar abscess, (2) perforation of the constrictor pharyngeus superior muscle, (3) parapharyngeal abscess, (4) acute cervical lymphadenitis and (5) phlebitis of the internal jugular vein.

Summary.—A septic temperature (96 to 106 F.), chills and sweats appeared in a patient immediately after a mild sore throat and persisted for twenty-six days. Transient slight swelling and tenderness at the angle of the jaw were the only signs of infection present. Operation revealed a retrotonsillar abscess with extension of the infection to the parapharyngeal space and phlebitis of the internal jugular vein. The patient was cured by tonsillectomy and ligation of the internal jugular vein.

Case 2.—H. H., a white man aged 51, previously in good health, became ill on Feb. 17, 1941 with malaise, muscular aches, chilliness, sweating and slight soreness of the left side of the throat. The oral temperature was 102 F.; the pulse rate was 110 and the respiratory rate 18 per minute. Physical examination disclosed only moderate congestion of the pharynx and slight swelling and redness of the left tonsil. The sore throat lasted two days. On the fourth day the patient began to have pain and slight swelling of the right knee, the left elbow and the metacarpal joints of the right middle finger. The involvement of these joints subsided within a week, but the fever persisted. The oral temperature ranged from 98 to 102 F. daily; the pulse rate was 70 to 110 per minute. There were no subjective symptoms other than anorexia, weakness, night sweats and loss of 15 pounds (6.8 Kg.) during the following month.

On March 18 slight soreness of the left side of the throat recurred and lasted two days. The pharynx was congested, but the tonsils showed no evidence of infection. The general physical examination gave completely negative results except for the development of a soft systolic murmur over the mitral area during the fifth week of illness. Repeated urinalysis failed to reveal any abnormalities. The white cells ranged from 11,000 to 13,000 per cubic millimeter of blood, with 80 to 85 per cent polymorphonuclears present.

On March 28 the patient was awakened from sleep by severe pain in the left side of the chest and difficulty in breathing. The pain lasted several hours and was increased by deep inspiration. The temperature rose to 103 F. Physical examination revealed a pleural rub, diminished breath sounds and impaired resonance at the base of the left lung. The signs of disease in the chest lasted four days and were associated with slight cough, but there was no hemoptysis. The temperature and sweating gradually subsided, and the condition of the patient slowly improved during the following week.

Between April 4 and April 11 there was no sweating or elevation of temperature. The slight systolic murmur at the mitral area persisted. The clinical diagnosis was acute rheumatic fever associated with mitral endocarditis and pleurisy.

On April 12 fever and sweating returned. The oral temperature ranged from 99 to 103 F. daily, and the pulse rate varied from 90 to 120 per minute. The patient received 60 to 90 grains (3.88 to 5.82 Gm.) of sodium salicylate daily. The medication had no effect on the patient's condition.

On April 24 a severe chill developed, followed by marked sweating. The oral temperature rose to 105 F., and the pulse rate was 140 per minute. Marked prostration was present. The clinical diagnosis of acute rheumatic fever seemed untenable. The possibility of subacute bacterial endocarditis was considered on account of the systolic mitral murmur, but there was no evidence of embolic phenomena or of enlargement of the spleen.

The patient was admitted to the hospital on April 28. The hemoglobin determination was 87 per cent; the red cells numbered 4,100,000 and the white cells from 9,700 to 14,600 per cubic millimeter of blood, with 75 to 80 per cent polymorphonuclears present. The urine was normal except for occasional red and white blood cells. Two blood cultures showed no growth. Agglutination tests for typhoid, paratyphoid, tularemia and undulant fever were negative. The Wassermann and Kahn tests of the blood were also negative. There was no evidence of malaria in the blood smears. Cutaneous tests with tuberculin were negative. A roentgenogram of the chest taken on April 30 revealed normal lungs and a normal heart. The patient received 60 grains of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) daily without any benefit.

Because a satisfactory explanation for the persistent fever was lacking, and because the fever had followed a mild but definite sore throat, the possibility of postanginal sepsis was first suspected on May 1, ten weeks after the onset of the illness. Examination of the neck revealed a localized area of tenderness at the angle of the left jaw but no swelling or induration. This finding had previously escaped recognition, probably because postanginal sepsis had not been considered and the neck had not been carefully examined.

On May 4 pain suddenly developed in the left lower region of the chest, with difficulty in breathing, followed by slight cough and slight hemoptysis. Physical examination revealed impaired resonance and diminished breath sounds over the lower lobe of the left lung. Roentgen examination revealed an elevation of the left side of the diaphragm and a triangular shadow in the lower lobe of the left lung typical of pulmonary infarction. It was felt that the entire clinical picture could be explained on a single basis, i. e., an infection in or around the tonsil, complicated by phlebitis of one of the veins of the neck and infarction of the lung. The patient was seen in consultation by Dr. Alexander Colwell, who advised tonsillectomy.

Tonsillectomy was performed on May 5 by Dr. J. McCready. As the left tonsil was removed, a large amount of pus welled up from the crypts. There was no pus behind the tonsil, and the superior constrictor pharyngeus muscle was intact. By cutting across the left tonsil an abscess cavity was found, measuring 8 by 8 mm., filled with pus. Microscopically, the wall of the abscess consisted of a slight amount of fibrous tissue infiltrated by polymorphonuclear and lymphocytic cells. The pus obtained from the abscess yielded growths of Streptococcus haemolyticus and Staphylococcus aureus on culture, but there was no evidence of the tubercle bacillus. The right tonsil showed no gross or microscopic evidence of infection.

The temperature ranged from 99 to 102 F. for four days after the operation. On the fifth day it returned to normal. The signs and symptoms of involvement of the chest slowly cleared up, and the patient's general condition improved during the following week. There was no further rise in temperature or recurrence of sweats. The cardiac murmur disappeared. The patient was discharged from the hospital on May 14 completely recovered. At the time of writing he has remained well for fourteen months.

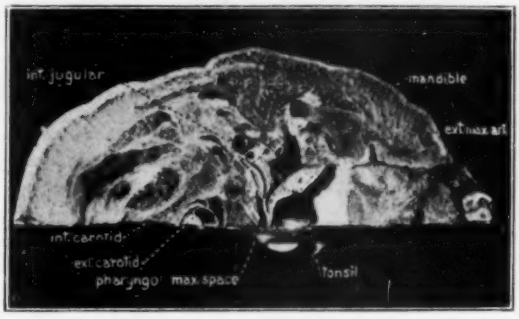
Summary.—A patient had night sweats and an intermittent fever (99 to 103 F.) for twelve weeks following mild pharyngitis and tonsillitis. Because of painful joints and a systolic mitral murmur, the condition was first incorrectly diagnosed as acute rheumatic fever. The patient had two bouts of pulmonary infarction during the fifth and twelfth weeks of his illness. Tenderness of the angle of the jaw was the only sign of infection. Operation revealed a small intratonsillar abscess. Recovery followed tonsillectomy, without ligation of the internal jugular vein.

BACTERIOLOGY

The organism most frequently associated with postanginal sepsis is an anaerobic streptococcus. Streptococcus viridans and Str. haemolyticus, Pneumococcus, Staphylococcus albus, Staph. aureus and an anaerobic bacillus have also been found in this lesion.[3]

ANATOMY

In order to understand the pathologic nature of this disease with its resultant clinical picture, an appreciation of the anatomy of the parapharyngeal space is important. This has been discussed fully by Mosher [4] and others.[5] In the accompanying photograph are shown the essential features of the parapharyngeal space. The latter is a connective tissue space that lies lateral to the pharynx and extends from the base of the skull to the angle of the jaw, a distance of 2.5 cm. It is separated medially from the tonsil by the superior constrictor pharyngeus muscle. The lateral border is formed by the internal pterygoid muscle, the ascending ramus of the jaw and the capsule of the parotid gland. The upper cervical vertebrae covered by the prevertebral muscles form the posterior boundary. The parapharyngeal space contains the ninth to twelfth cranial nerves, a few lymphatic glands, the



Horizontal section of the head at the level of the tonsil (after Hall [5a]).

internal carotid artery and the internal jugular vein. It communicates with the cranium through the carotid canal and the jugular foramen and with the mediastinum by the carotid sheath.

PATHOGENESIS AND PATHOLOGY

The source of this disease is usually an infection in or about the tonsils.[1] The disease may occur during or after an acute abscess of the throat,[6] such as an intratonsillar, a peritonsillar, a retrotonsillar or a retropharyngeal abscess, or it

3. (*a*) Beck, A. L.: Deep Neck Infection, Ann. Otol., Rhin. & Laryng. **48**:940 (Dec.) 1939. (*b*) Hirsch, C.: Septicemia Following Tonsillitis, New York State J. Med. **35**:767 (Aug. 1) 1935. (*c*) Reye, E.: Zur Pyämie nach Angina, Med. Welt **4**:1791 (Dec. 13) 1930.

4. Mosher, H. P.: Deep Cervical Abscess and Thrombosis of the Internal Jugular Vein, Laryngoscope **30**:365 (June) 1920.

5. (*a*) Hall, C.: The Parapharyngeal Space, Ann. Otol., Rhin. & Laryng. **43**:793 (Sept.) 1934. (*b*) Shapiro, S. L.: Deep Cervical Infection Following Tonsillectomy, Arch. Otolaryng. **11**:201 (June) 1930.

6. (*a*) Deering, W., and Brennemann, J.: Acute Abscess of the Throat, J. A. M. A. **118**: 1171 (April 4) 1942. (*b*) Beck, A. L.: A Study of Twenty-Four Cases of Neck Infection, Tr. Am. Acad. Ophth. **37**:342, 1932. (*c*) Haymann, L.: Erhebungen über die tonsillogene Sepsis, Ztschr. f. Hals-, Nasen- u. Ohrenh. **35**:288, 1934.

may follow mild tonsillitis or pharyngitis.[7] In a small percentage of the cases it follows tonsillectomy [8] and infections of the ear, adenoids, the floor of the mouth, a jaw, a cervical vertebra, a parotid gland, the nose, the paranasal sinuses or the mastoid.[9]

In most cases of postanginal sepsis, as in case 1, the infection extends from the throat through a constrictor pharyngeus muscle to produce cellulitis or an abscess in the parapharyngeal space.[10] Phlebitis of the internal jugular vein is apt to occur as a result of invasion of the wall of the vein by the infection present in the parapharyngeal space.[11] In a small percentage of reported cases, as apparently in case 2, there is no pus in the parapharyngeal space; the lesion is primarily phlebitis of the small veins of the tonsil, which may extend through the facial vein to involve the internal jugular vein.[12] Whether the lesion involves the internal jugular vein together with its tributaries, or whether the phlebitis is limited to the tonsillar,[13] the facial [14] or the internal jugular vein,[15] the end result is the same: The organisms directly invade the blood stream.

A review of 105 reported cases reveals that the degree of phlebitis noted at operation or at autopsy varies from slight microscopic changes in the wall of a patent vein [16] to the characteristic whitened and thickened vein containing an adherent purulent thrombus.[17] In some instances, as in case 1, a whitened, thickened vein containing fluid blood or fluid pus may be observed or there may be suppurative periphlebitis.[18]

An analysis of clinical and postmortem observations indicates that there is no definite correlation between the degree or extent of phlebitis and the severity of the symptoms. Severe septicemia may occur with slight or marked phlebitis, with or without thrombosis.[19] Thrombosis is important, however, since infected thrombi are frequently responsible for septic infarcts of the lung.[20] From these infarcts, or as a result of the direct passage of bacteria through the pulmonary capillaries, metastatic abscesses may occur in other parts of the body.

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7. (*a*) Kissling, K.: Ueber postanginöse Sepsis, München. med. Wchnschr. **76**:1163 (July 12) 1929. (*b*) Hall, C.: Sepsis Following Pharyngeal Infections, Ann. Otol., Rhin. & Laryng. **48**:905 (Dec.) 1939. Hirsch.[3b]

8. (*a*) Reuben, M. S.: Postanginal Sepsis, Arch. Pediat. **52**:152 (March) 1935. (*b*) Shapiro.[5b]

9. (*a*) Beck, A. L.: Parapharyngeal Infections and Internal Jugular Vein Thrombosis: Diagnosis and Treatment, Laryngoscope **44**:431 (June) 1934. (*b*) Reuben.[8a]

10. (*a*) Waldapfel, R.: Post-Tonsillitis Pyemia, Tr. Am. Acad. Ophth. **33**:291, 1928. (*b*) Hirsch.[3b]

11. (*a*) Dixon, O. J., and Helwig, F. C.: Thrombophlebitis of the Internal Jugular Vein as a Complication of Tonsillitis, Ann. Otol., Rhin. & Laryng. **39**:1137 (Dec.) 1930. (*b*) Joel, W.: Ueber die postanginöse Pyämie und ihre Verbreitungswege, Deutsche med. Wchnschr. **55**:2133 (Dec. 20) 1929. Hirsch.[3b] Mosher.[4] Hall.[7b]

12. Fraenkel, E.: Pyämie nach Angina, Deutsche med. Wchnschr. **52**:93 (Jan. 15) 1926. Waldapfel.[10a]

13. Hall.[7b] Beck.[9a] Waldapfel.[10a]

14. Knick: Die operative Heilung der tonsillären Sepsis, Ztschr. f. Hals-, Nasen- u. Ohrenh. **18**:546, 1927-1928.

15. Waldapfel.[10a] Dixon and Helwig.[11a]

16. Burchardt.[2c] Beck.[6b] Knick.[14]

17. Hirsch.[3b] Mosher.[4] Dixon and Helwig.[11a]

18. (*a*) Bertelsmann, R.: Ueber Postanginöse Sepsis sive Bakterämie, Zentralbl. f. Chir. **54**:642 (March 12) 1927. (*b*) Rubin, H.: Pyemia Following Acute Tonsillar Infections, Arch. Otolaryng **17**:183 (Feb.) 1933. Kissling.[7a]

19. Bertelsmann, R.: Postanginöse Sepsis und die Lymphbahnen, Zentralbl. f. Chir. **54**: 1949 (July 30) 1927. Beck.[6b] Hall.[7b]

20. Kissling.[7a] Dixon and Helwig.[11a]

CLINICAL FEATURES

The onset of the disease is often insidious, beginning with a mild infection of the upper respiratory tract.[21] The sore throat may be slight and fleeting, as in the reported cases, and easily overlooked. On the other hand, the disease may be ushered in with severe symptoms when a marked infection is present in the throat.

The symptoms of this condition may be divided into two categories: (1) local and (2) systemic.

The local symptoms—pain, trismus, torticollis, dysphagia or hoarseness—are due to the primary infection of the throat, to the parapharyngeal abscess or to both. Although local symptoms are usually present, it is important to remember that they may be transient or completely absent, as in the patients described in a foregoing section of this paper.[7b] The absence of local symptoms is deceptive and often responsible for diagnostic errors.

The systemic symptoms are due principally to suppurative phlebitis of the internal jugular vein or of one of its tributaries. The symptoms vary, depending on the virulence of the infecting organisms. They may occur during or immediately after the infection of the throat, or they may be delayed as long as sixty days after the primary infection has healed.[6b] The average patient has a latent or asymptomatic period of fourteen days between the infection of the throat and the appearance of sepsis.

The systemic symptoms are those of any septicemia: high fever, chilliness or chills, sweating, rapid pulse, rapid respiration and prostration, with or without delirium. A review of the cases reported in the literature reveals two types of temperature curves: (1) The fever may be of the septic type and associated with chills; (2) a continuous high temperature may be present without chills. In unusual instances,[3c] as in case 2, a low grade or moderate fever, with or without remissions, may be present a number of weeks before high fever and chills develop. It is important to note that chills or positive blood cultures have appeared in only 50 per cent of the reported cases.[22] Their absence, therefore, is of no diagnostic importance. Jaundice [18b] is not unusual and is probably due to damage of the liver or to hemolysis of red blood cells. The spleen may be enlarged and palpable. Lesions of the skin, such as petechiae or purpura, may be present.[6a] Pain [18b] may occur in the joints, as in case 2, and simulate acute rheumatic fever. Secondary anemia usually develops. The leukocyte count has varied from 5,000 to 60,000 in the reported cases, and usually there has been an increase in the polymorphonuclear cells. Albuminuria is common. Hematuria [23] may occur as a result of infarction of the kidney or of complicating nephritis.[18b]

There may be symptoms referable to the hypoglossal, glossopharyngeal, vagus or accessory nerves as a result of extension of the infection to these nerves as they pass through the parapharyngeal space.[3b]

Sooner or later grave complications occur. Fatal hemorrhage has been reported in parapharyngeal infection, due to erosion of the internal or the external carotid artery.[24] The infection may extend down the carotid sheath to the mediastinum to produce severe dyspnea or asphyxia.[3a] The most frequent complications are pulmonary; infarction, abscess, pneumonia or empyema.[25] Metastatic abscesses of the

21. Hirsch.[3b] Beck.[6b] Hall.[7b]

22. Hirsch.[4b] Beck.[9a]

23. Matis, E. I.: Two Unusual Cases of Postanginal Sepsis, Ann. Otol., Rhin. & Laryng. **49**:559 (June) 1940.

24. Salinger, S., and Pearlman, S. J.: Hemorrhage from Pharyngeal and Peritonsillar Abscess, Arch. Otolaryng. **18**:464 (Oct.) 1933.

25. Kissling.[7a] Dixon and Helwig.[11a] Knick.[14]

bones, the joints, the muscles, the brain, the liver and the kidneys are common. Meningitis or infection of a cavernous sinus with ocular symptoms has occurred in 10 per cent of the fatal cases. Such developments are due to retrograde extension of the phlebitis and involvement of the jugular bulb and the sigmoid sinus or of the pterygoid plexus and the ophthalmic vein in this condition.[26] These complications may obscure and prevent diagnosis of the primary disease.

The disease pursues a highly variable course. It may continue for periods between a few days and several months, depending on the severity of the sepsis and the presence or the absence of complications.[27] Death occurs in almost 100 per cent of the cases if the condition is unrecognized and untreated.[26b]

DIAGNOSIS

As with other diseases, postanginal sepsis is often overlooked either because the physician is unfamiliar with its varying manifestations or because he fails to consider such a diagnosis. It has been estimated that of every 100 cases in which death occurred from this disease, in only 20 was the condition recognized during life.[28]

The development of septicemia or pyemia during or after an infection of the throat should suggest the possibility of suppurative inflammation of the veins of the neck. As a rule, the presence of an infection of the throat is evident from the history and the physical signs, but occasionally there may be no clue to the source of the sepsis. The initial infection may be slight and fleeting,[21] or it may be present weeks before the onset of sepsis,[6b] and thus it may be completely overlooked. In addition, there may be no local signs or symptoms to direct attention to the throat when the patient comes under observation with a septic temperature, chills or metastatic symptoms.[29] The condition usually passes under the guise of septicemia of unknown origin[1]; the primary disease is overlooked during life and first recognized at postmortem examination.

Provided the possibility of postanginal sepsis is considered, the diagnosis may be made for every patient presenting the clinical picture of septicemia of pyemia of unknown origin. Sepsis from other causes, such as diseases of bone or of the ear or acute bacterial endocarditis, must of course be excluded. In the absence of any demonstrable cause of sepsis, a history of recent inflammation of the throat, however slight, must always lead to the suspicion of phlebitis of the internal jugular vein or of one of its branches. Slight swelling of the lateral wall of the pharynx or displacement or swelling of the tonsil may be additional evidence of this disease,[6b] but the absence of these signs is of no diagnostic value.[30] In the presence of a normal throat the diagnosis must rest on the history of an infection of the throat plus a careful examination of the neck of the patient. The involved vein is rarely palpable,[29] but swelling,[18b] tenderness[31] or induration[32] may occur along the

26. (*a*) Long, J. W.: Excision of Internal Jugular Vein for Streptococcic Thrombi Vein and Cavernous Sinus Causing Paralysis of Orbital Muscles, Surg., Gynec. & Obst. **14**:86, 1912. (*b*) Claus, H.: Acht und zwanzig Fälle von Pyämie nach Angina, Ztschr. f. Hals-, Nasen- u. Ohrenh. **21**:114, 1929. (*c*) Hirsch.[3b] (*d*) Rubin.[18b]

27. (*a*) Stahl, R.: Zur Kenntis der Thrombophlebitis und Sepsis postanginosa, Deutsche med. Wchnschr. **53**:186 (Jan. 28) 1927. (*b*) Fraenkel.[12]

28. Mlechlin, B., cited by Matis.[23]

29. Claus, H.: Bemerkungen zur Pyämie nach Angina, Ztschr. f. Hals-, Nasen- u. Ohrenh. **18**:557, 1927. Hall.[7b] Claus.[26b]

30. Hall.[7b] Claus.[26b] Claus.[29]

31. Hall.[7b] Beck.[9a] Rubin.[18b] Matis.[23]

32. Goodman, C.: Primary Jugular Thrombosis Due to Tonsil Infection, Ann. Otol., Rhin. & Laryng. **26**:527, 1917.

anterior border of the sternocleidomastoid muscle. Occasionally, there may be some swelling of the parotid gland with infection of the parapharyngeal space.[33] These signs, however, are frequently absent in patients with phlebitis or thrombosis of the internal jugular vein,[34] so that they cannot be relied on constantly in diagnosis. Tenderness at the angle of the jaw on the involved side, with or without slight swelling, may be the only presenting sign.[35] This sign is present in most if not all cases,[29] but it may be transient, as in case 1. Unless the disease is kept in mind and the neck and the throat carefully and repeatedly examined, the source of the sepsis may not be discovered. Minor evidence of infection should suffice for the diagnosis, particularly when all other causes of septicemia have been ruled out. To wait for the development of marked edema or tenderness in the presence of relatively slight but definite signs may prove fatal.[6b] To wait for a positive blood culture may also be fatal, since in this condition cultures are frequently found negative.[36]

DIFFERENTIAL DIAGNOSIS

A review of the literature reveals the fact that many patients with this condition have died with the clinical diagnosis of "septicemia of unknown origin" [1] or with a diagnosis suggesting that the disease has been confused with a number of other diseases. The more important of these are pneumonia, thrombosis of a lateral sinus, acute or subacute bacterial endocarditis, acute renal infection, blood dyscrasia, acute osteomyelitis and meningitis.

Pneumonia.—Metastatic lesions of the lungs (infarction or abscess) are common in postanginal sepsis and have often been confused with pneumonia.[7b] In differentiating these conditions, the history and the sequence of events are important. The history of attacks of "pleurisy" or "pneumonia" during or after an infection of the throat, as in case 2, should suggest the possibility of phlebitis of a vein of the neck with pulmonary metastasis. A careful search must be made of the neck and the throat for evidence of this condition. Septicema or pyemia may occur in pneumonia, but there is usually clearcut evidence of a severe pulmonary infection from the start. The reverse holds true for postanginal sepsis, in which signs and symptoms of septicemia precede involvement of the lungs.

Thrombosis of a Lateral Sinus.—Postanginal sepsis may be mistaken for thrombosis of a lateral sinus when suppuration of the middle ear complicates an acute infection of the throat.[18b] Signs and symptoms of sepsis, a positive blood culture and changes in the eyegrounds are common to both conditions. Clinical or roentgen evidence of acute mastoiditis is indicative of thrombosis of a lateral sinus. In the absence of mastoiditis pain, swelling or tenderness of the neck or the throat is highly suggestive of postanginal sepsis. When the infection of the middle ear and throat occur on the same side, a positive Tobey-Ayer test is of no value in differential diagnosis, since an occluding thrombus of the internal jugular vein may occur in either condition. With otitis on the side opposite the infection of the throat, a positive Tobey-Ayer test may be of localizing or diagnostic value.[18b] A negative test is, however, of no diagnostic importance, since the test is negative with simple phlebitis, with a mural thrombus of the internal jugular vein or with thrombophlebitis of the tonsillar or the facial vein.

Acute or Subacute Bacterial Endocarditis.—The local evidence of postanginal sepsis may be slight and overshadowed by septicemia. Soft mitral systolic murmurs

33. Abt.[2a] Beck.[3a]
34. Beck.[6b] Stahl.[27a]
35. Hall.[7b] Claus.[29]
36. Hirsch.[3b] Hall.[7b] Beck.[9a] Claus.[26b]

may occur in the absence of endocarditis as a result of fever or anemia. In such instances, as in case 1, the presence of severe septicemia and a functional cardiac murmur may lead to the incorrect diagnosis of acute bacterial endocarditis. The differentiation between septic phlebitis of a vein of the neck and acute bacterial endocarditis may be extremely difficult. A recent infection of the throat may antedate both conditions. The development, however, of embolism or of a murmur pathognomonic of valvular heart disease points to acute bacterial endocarditis.[37] The development of tenderness or swelling of the neck, as in the reported cases, may be the only clue to postanginal sepsis. If the condition is unrecognized, bacteria entering the general circulation may produce acute bacterial endocarditis.[38]

Fever, chills, Str. viridans septicemia, a palpable spleen, secondary anemia, the presence of red blood cells in the urine and a systolic murmur may be noted in a patient with postanginal sepsis and may simulate subacute bacterial endocarditis. It is well known that a cardiac murmur does not necessarily point to the diagnosis of subacute bacterial endocarditis, although the absence of a murmur is strong evidence against such a diagnosis. Subacute bacterial endocarditis is differentiated from postanginal sepsis by the presence of chronic valvular or congenital heart disease and embolic phenomena.

Acute Renal Infections.—Pain and tenderness in the loin may occur in a patient with postanginal sepsis as a result of metastatic abscess and may suggest acute pyelonephritis or carbuncle of the kidney. The urine reveals acute pyelonephritis if this is present. A history of fever or chills antedating the pain in the loin is suggestive of general sepsis with metastatic involvement of the kidney rather than of a primary abscess of the kidney.

Blood Dyscrasia.—A sudden onset of sore throat, septic fever, chills, marked prostration and an edematous or ulcerative lesion of the tonsil or throat may occur with acute leukemia or agranulocytic angina and may simulate a primary infection of the throat with sepsis. Septicemia, on the other hand, may be associated with a leukemoid reaction or a state of marked leukopenia that may be confused with a blood dyscrasia. The correct diagnosis will rest on the clinical examination plus a study of a blood smear. Although myelocytes are common in sepsis, most of the white cells are metamyelocytes and mature polymorphonuclears, in contrast with the blood picture of acute leukemia, in which most of the cells are myeloblasts, with an occasional myelocyte present.[39] In overwhelming sepsis the bone marrow may be depressed to the point of leukopenia but rarely to that of agranulocytosis.[40] Differentiation between the agranulocytosis of sepsis and true agranulocytic angina may be difficult or impossible if the patient is seen late in the course of the disease. In sepsis the signs and symptoms of infection precede the fall in the white blood cell count. In agranulocytic angina the reverse is observed.

Acute Osteomyelitis.—Acute osteomyelitis may be secondary to septicemia associated with phlebitis of the internal jugular vein. If the signs and symptoms of osteomyelitis dominate the clinical picture, the infection of the neck may be com-

37. White, P. D.: Heart Disease, ed. 2, New York, The Macmillan Company, 1931, p. 344.

38. Artuse, C., cited by Abt.[2a]

39. Kracke, R. R., and Garver, H. E.: Diseases of the Blood and Atlas of Hematology, with Clinical and Hematologic Descriptions of the Blood Diseases Including a Section on Technics and Terminology, Philadelphia, J. B. Lippincott Company, 1937.

40. (*a*) Bigler, J. A., and Brennemann, J.: Sepsis with Leukopenia (Agranulocytosis) in Children, Am. J. Dis. Child. **40**:515 (Sept.) 1930. (*b*) Jackson, H.: Agranulocytic Angina and Allied Conditions, Internat. Clin. **3**:68 (Sept.) 1933.

pletely overlooked. A history of recent soreness of the throat, fever and chills antedating the osteomyelitis should suggest the possibility of septicemia with metastatic involvement of the bone. A careful search must be made for a primary infection of the parapharyngeal space.

Meningitis.—Involvement of the central nervous system may occur in the course of postanginal sepsis and suggest primary meningitis or meningoencephalitis.[7b] The diagnosis rests on a careful clinical examination plus studies of the blood and the spinal fluid.

TREATMENT

The treatment is surgical intervention. This must come early, before the development of metastatic abscesses in the viscera. Because time is so important, exploratory incision with the region under local anesthesia is indicated if the diagnosis is doubtful. It is generally agreed that the parapharyngeal space should be drained externally and the jugular vein ligated or excised,[41] although recovery has occurred by drainage of the abscess without ligation or resection of the vein.[2b] Some observers have expressed the belief that tonsillectomy should be performed in addition to the operation on the neck.[42] In the cases reported in this paper tonsillectomy proved life saving, probably because the abscess was either drained or removed by this procedure.

Chemotherapy as a supplement to surgical treatment may be of value in combating this condition.

CONCLUSIONS

Postanginal sepsis is a definite clinical entity that demands early diagnosis and operation to prevent death. This disease is due to suppurative inflammation of the internal jugular vein or of one of its tributaries. The possibility that it is present must be considered in every case of septicemia of unknown origin. The diagnosis is easy to make if the following sequence of events is considered: (1) An infection of the throat has occurred, according to the history or evidence from examination; (2) a state of septicemia or pyemia has developed. A latent period may or may not have elapsed between the infection and the time of onset of sepsis. A definite diagnosis may be made on finding tenderness, swelling or induration of the neck in a patient presenting the characteristic clinical picture, provided all other causes for sepsis are first ruled out. Swelling of the lateral wall of the pharynx or displacement or swelling of the tonsil may be additional evidence of this disease, but the absence of these signs is of no diagnostic importance.

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41. Mosher.[1] Beck.[6b] Claus.[26b] Claus.[29]
42. Beck.[3a] Beck.[9a] Claus.[26b]

Progress in Internal Medicine

BLOOD

A REVIEW OF THE RECENT LITERATURE

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The number of important investigations on hematologic subjects recently reported is surprising in view of wartime conditions. Many of the contributions, of course, relate to work undertaken and largely completed before the entrance of the United States into World War II, but there is abundant and gratifying evidence that, in spite of necessary curtailments, significant research continues to be carried on in many centers throughout the country.

Of special interest are reports from Great Britain indicating a relationship between diminished hemoglobin in women and children and restrictions of diet imposed by present conditions. It should be appreciated that anemia in such conditions is likely to be but one manifestation of the impaired nutritional status, and the situation presents a challenge to medical and public health authorities to provide instruction relative to securing adequate amounts of essential nutrients from available food materials.

PERNICIOUS ANEMIA AND RELATED MACROCYTIC ANEMIAS

A number of important papers dealing with pernicious anemia appeared during 1942. Of these, the most significant is that of Fox and Castle,[1] who report that in human beings the intrinsic factor is secreted by the glands in the fundus of the stomach rather than chiefly by those in the pyloric region, as in swine. Other articles of special interest which deal with various aspects of pernicious anemia and other macrocytic anemias are concerned with: the relation of solar radiation to the incidence of pernicious anemia; the chemical composition of the antipernicious-anemia factor in liver; the changes in the bone marrow; the relation between pernicious anemia and cancer of the stomach; the spontaneous occurrence in monkeys of a condition simulating subacute combined degeneration of the spinal cord; the presence of hypoprothrombinemia in pernicious anemia; the

1. Fox, H. J., and Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: Difference in Site of Secretion of Intrinsic Factor in the Hog and in the Human Stomach, Am. J. M. Sc. **203**:18, 1942.

advantages of the intramuscular treatment and the tendency to prolong the interval between maintenance doses to four weeks or longer; the relation of a deficiency of vitamin C to relapse in patients with pernicious anemia during the spring months; the possibility that polycythemia may result occasionally from liver therapy; in general, the failure of methods for the assay of liver extracts, except that of administering them to patients with pernicious anemia; and the illuminating studies on the cause of the disease which have been developed since Castle's earliest contributions.

Etiology.—(*a*) Role of Changes in the Gastrointestinal Tract: Fox and Castle confirm the observations of Meulengracht,[2] of Magnus and Ungley [3] and others that desiccated portions of the fundus of the hog stomach were devoid of antipernicious-anemia activity, whereas those of the pyloric region displayed it. Furthermore, they obtained supporting evidence that the distribution of the material with blood-forming activity coincides with the site of secretion of the intrinsic factor. Their studies on the hemopoietic effect of desiccated human stomach led to the important conclusion that there is in the latter a distinctly different distribution of the active substance as compared with that in the hog stomach. Thus, preparations of the so-called fundic and cardiac areas of the human stomach were highly effective, whereas that of the pyloric area was only weakly active. This led the authors to conclude that in man, not the pyloric region of the stomach, but the areas designated as the "fundus" and the "cardia," are the important sites of the formation or secretion of the intrinsic factor. In their minds there is no question that in the human stomach it is the type of gland that is found in the fundus that is associated with antianemia activity. This observation is important, since it is in accord with the observation that in cases of pernicious anemia the fundus of the stomach undergoes degeneration. Furthermore, if the "pyloric gland organ" is not an important site of the formation of the intrinsic factor, it is readily understood why the blood picture of pernicious anemia does not develop following partial resection of the stomach in human beings, and why the pure duodenal secretion in man does not contain detectable amounts of the intrinsic factor.

Cox,[4] in a study of the stomach in 6 cases of pernicious anemia in which necropsy was performed, found extensive changes in the mucosa, similar to those described in this disease by Meulengracht and others. These alterations were sharply delimited from the pyloric zone and could be distinguished from other types of "gastritis." The changes suggested injury to the specific secretory cells of the body and fundus of the stomach, with repair by less differentiated epithelial cells. According to the author, there was no evidence of a return to normal in the cases in which there had been prolonged therapy. In 1 case of sprue significant gastric lesions were not shown. It was concluded that the gastric changes in pernicious anemia were not the result of the anemia but may have represented a true etiologic relationship.

It is stated by Petri, Bing, Nielsen and Kjerbye [5] that various attempts have been made to determine the etiologic relationship of the status of different parts

2. Meulengracht, E.: Histologic Investigation into Pyloric Gland Organ in Pernicious Anemia, Am. J. M. Sc. **197**:201, 1939.

3. Magnus, H. A., and Ungley, C. C.: Gastric Lesion in Pernicious Anaemia, Lancet **1**:420, 1938.

4. Cox, A. J.: The Stomach in Pernicious Anemia, Am. J. Path. **18**:782, 1942.

5. Petri, S.; Bing, J.; Nielsen, E., and Kjerbye Nielsen, A.: Deficiency of Antipernicious Anemia Principle in Liver Extract from Swine After Elective Resection of Fundus of Stomach: Clinicotherapeutic Study, Acta med. Scandinav. **109**:59, 1941.

of the gastrointestinal tract to the development of pernicious anemia. These attempts may be summarized as follows: In swine the intrinsic factor is localized to the cardiac, pyloric and duodenal regions, and the cells concerned are designated as the "pyloric gland organ" by Meulengracht. Sufficient investigation has not been made of the intestinal tract as a site for the interaction of the intrinsic and extrinsic factors and the absorption of the product thus formed. On the other hand, it is recognized that in patients with pernicious anemia the fundus of the stomach is the chief site of the pathologic changes in the mucous membrane. Finally, it is stated that even removal of the entire region assigned to the intrinsic factor and the distal part of the intestine in dogs has not produced pernicious anemia in these animals. It is also noted that resections of the stomach and duodenum in man give rise to this form of anemia only in exceptional cases. In an effort to obtain new information, various areas of the hog stomach were resected, and after a considerable period the liver was removed and a liver extract prepared. This was administered to patients with pernicious anemia, in an assay of potency. The authors found that total gastrectomy performed on swine eleven months previously brought about a complete absence of the antipernicious-anemia principle in the liver. In 3 animals, selective resection of the fundus caused, in periods of one hundred and sixteen, two hundred and fifty-eight and three hundred and seventy-nine days, a reduction or a complete loss of the principle. The authors consider that they have demonstrated a relationship between the fundus of the stomach and the amount of the specific principle in the liver in swine. It is their opinion that this is concerned with the utilization of the extrinsic factor by the organism.

Petri, Jensenius and Thyssen [6] conclude, after extensive experimental studies on dogs, that operative elimination of the pyloric and Brunner gland area in the duodenum, thought by some to be the sites in which the intrinsic factor is elaborated, did not result in experimental pernicious anemia. It did cause a severe pellagrous symptom complex in young dogs and a mild subpellagrous condition in older animals. In addition, resection of the pyloric region, the Brunner gland region and the distal two thirds of the small intestine in 3 pups did not produce a regular state of pernicious anemia. On the other hand, these pups showed arrest of growth, emaciation, alterations in the skin and the hair and degenerative changes in the nervous system. In 2 of the 3 animals there appeared hyperchromic macrocytic anemia and attacks of diarrhea. It was the authors' conclusion that pernicious anemia was not produced, because (1) the operative procedure did not jeopardize the formation of the intrinsic factor, (2) it was not sufficiently extensive and (3) the prevailing conception of the intrinsic factor and of the way in which the liver principle is formed is erroneous.

Olivia and Pitzurra [7] fed a patient with pernicious anemia 100 Gm. of raw chopped beef and removed it from the stomach after one hour. Subsequently, the patient responded adequately to the therapeutic test of intramuscular liver extract. The stomach content thus obtained was brought to a p_H of 7.5, incubated and filtered, and was then administered to a second patient with pernicious anemia. This patient showed lessening of the diarrhea, diminution of the glossitis and a

6. Petri, S.; Jensenius, H., and Thyssen, E.: Experimental Studies on Production of Pernicious Anemia by Operation on the Digestive Tract: Results of Combined Elective Resection of the Pylorus and the Brunner-Gland Section of the Duodenum and the Distal ⅔ of the Small Intestine (on Pups), Acta med. Scandinav. **107**:532, 1941.

7. Olivia, G., and Pitzurra, M.: Reticulocytenfördende und antiperniziöse Wirkung der Komplexes, "perniziöser Magensaft Fleich" in Krankheitsfallen von perniziöser Anämie, Klin. Wchnschr. **21**:733, 1942.

striking increase in the reticulocytes of the circulating blood. The marrow showed no changes. A second patient who received a similar injection improved, but not so strikingly. It was assumed that the reaction between the gastric juice of a patient with pernicious anemia and meat did not produce the active anti-pernicious-anemia principle but that it did result in the formation of something which stimulated a reticulocyte rise. The authors conclude that there are two distinct physiologic substances which stimulate erythropoietic functions, one for the formation of red blood cells and the other for the production of reticulocytes.

Crandall,[8] in an article dealing primarily with the effects of the absence of bile from the gastrointestinal tract, makes the rather startling claim that by the establishment of a bile fistula he is able to produce a macrocytic type of anemia resembling pernicious anemia in many respects. According to him, the blood picture is of the macrocytic, hyperchromic type; it is associated with hyperplasia of marrow erythroblasts; it shows a response to parenteral injection of liver extract, and, finally, it shows no response to any substance or dietary factor other than that which is effective in pernicious anemia. It is his opinion that an absence of bile from the gastrointestinal tract produces a deficiency of the anti-pernicious-anemia factor in the body because of a failure of absorption of this substance. These statements are important because, if confirmed, they indicate that a type of anemia has been produced in the dog which closely resembles pernicious anemia in human beings.

A brief but accurate and well presented résumé of the role of the stomach in the etiology of pernicious anemia is given as an unsigned leading article in the *British Medical Journal*.[9] After stating the essential facts of the historical development of knowledge in this field, the author comments favorably on the work of Fox and Castle,[1] in which the apparent discrepancy between the anatomic and the biochemical changes in the stomachs of patients with pernicious anemia is explained. It is remarked that the work of these investigators has shown that there is no discrepancy but "that the mistake lay in the unnatural identification of pigs with men," which in this instance, at least, was unjustifiable. It is very properly emphasized again that an inference is dangerous when drawn from one species and applied to another. The article shows the difficulties with which investigators in this field are forced to contend, owing to the fact that they are confined to work on human subjects with the disease. It is considered by the author that work bearing on the mechanism of pernicious anemia has languished during the past five years for at least four reasons: lack of a suitable animal for experimental work; lack of a laboratory test for the liver principle; the relatively intractable nature of the materials in which the intrinsic and extrinsic factors are located, and the doubt whether the liver principle can be elaborated by interaction of the intrinsic and extrinsic factors in vitro.

Weiss and Foldes[10] give an extensive and detailed discussion concerning the interrelationship between the digestive system and the morphologic picture and the chemical composition of the blood, with the greater amount of emphasis on the latter. A schematic arrangement is presented which shows the many changes of the blood found in association with changes in the functional and organic state of the gastrointestinal tract, the liver and the pancreas. It is emphasized that

8. Crandall, L. A., Jr.: Effects of Absence of Bile from Gastrointestinal Tract, Memphis M. J. **17**:114, 1942.

9. The Stomach in Pernicious Anemia, editorial, Brit. M. J. **1**:765, 1942.

10. Weiss, S., and Foldes, E.: The Digestive System and the Blood: Interrelationship Between the Digestive System and the Morphologic and Chemical Composition of the Blood, Internat. Clin. **1**:234, 1942.

many of the changes in the blood are conditioned by states of the digestive system and that, on the other hand, the digestive system may be influenced by the composition of the blood.

Joll and Adler [11] give a brief review, with a report of 2 cases of long survival after total gastrectomy, which is of interest relative to the role of the stomach in the etiology of pernicious anemia. The article deals with 135 reported cases of total gastrectomy, which is defined rigidly as removal of the whole stomach so that in the specimen are found a portion of esophagus at one end and a portion of duodenum at the other. Such a concise and precise definition surely offers no possibility of misunderstanding. Such cases are of special interest because the operation produces in many respects an ideal experimental situation in which to evaluate the relation of the stomach to addisonian pernicious anemia. Yet, as Chester Jones said in his admirable review on this subject, published in 1940, "the development of serious anemias is not to be feared. An occasional macrocytic or microcytic anemia ensues in the course of months." Jones concluded, according to these authors, that extragastric lesions must coexist for the production of addisonian pernicious anemia following total gastrectomy, possibly due to the destruction of argentaffin cells in the duodenum, small intestine, colon and appendix. Furthermore, in Jones's opinion an adequate and well balanced diet should suffice to prevent occurrence of anemia. With improved surgical technic and skill, it is likely that in the future complete gastrectomy will be performed successfully in an increased number of cases. In all such cases careful studies of the blood should be done, including hematocrit determinations, in order that, among other estimations, the cell volume may be determined at intervals. Now that Fox and Castle have demonstrated that the cells secreting the intrinsic factor are probably in the fundus of the stomach, it would be logical to expect that total gastrectomy would be followed by macrocytic anemia. There must be attached to this statement, however, some qualifying provisions. Such anemia should develop, provided the patient survives long enough and provided no other portions of the gastrointestinal tract can assume in totality the anti-pernicious-anemia function of the glands of the fundus. It has been shown that the duodenal secretion does not contain the intrinsic factor and that any activity in the ileum is in all probability due to the erythrocyte-maturing factor retained in the walls of the small intestine while it is en route to being absorbed by the portal system. The relatively brief period of survival following total gastrectomy is probably the greatest deterrent to the development of macrocytic anemia. In the reported cases the average duration of life is well under two years, and almost all patients die of metastases. The 2 patients whose cases are presented by the authors survived three years and two months, and three years and six months, respectively. Each had, both before and after the operation, moderately severe anemia, which appeared to be of the type associated with chronic hemorrhage rather than pernicious anemia.

A comprehensive discussion of achlorhydria and its ultimate significance is given by Crohn,[12] but reference will be made here only to that part concerned with the relation of achlorhydria to pernicious anemia. He emphasizes that at any decade of life a certain percentage of the normal population has achlorhydria; the incidence begins in childhood and increases with each decade up to the age of 60 years. He states that there is no explanation for this finding at present.

11. Joll, C. A., and Adler, D. I.: Long Survival After Total Gastrectomy: A Brief Review, with a Report of Two Cases, Brit. M. J. **2**:632, 1942.

12. Crohn, B. B.: Achlorhydria: Its Ultimate Significance, Tr. A. Life Insur. M. Dir. America **28**:74, 1942.

No histologic abnormality is present to account for the achlorhydria which is found in an average of 5 per cent of the population. He regards anacidity as asymptomatic except in a very small percentage of these persons, in whom it may cause diarrhea. He believes that complete anacidity, or achylia gastrica, is an essential part of the syndrome of pernicious anemia but concedes that "occasionally" one meets with a patient who has persistent secretion of hydrochloric acid. We are not in accord with this statement, for we regard the so-called pernicious anemia in a patient with hydrochloric acid in the gastric secretions as due to some cause other than deficiency of the intrinsic factor of Castle. In the opinion of Crohn, the achlorhydria in patients with pernicious anemia is associated, in most instances, with true atrophic gastritis, which does not change when a remission is induced by anti-pernicious-anemia medication. In his opinion, insufficient data are at hand to say how many patients with asymptomatic achlorhydria will ultimately have some type of anemia. He warns that if a person has anacidity and has a blood relative with pernicious anemia, the situation constitutes an added risk from the standpoint of insurance. With the uncertainty as to whether a person with achlorhydria will have pernicious anemia, and with available potent therapy, such a risk is surely not a great one, and, moreover any conclusion in regard to it should be based on a study of the length of life of patients with pernicious anemia and of the longevity of their blood relatives. Certainly, from a theoretic standpoint there is no reason why a patient with pernicious anemia should not survive for the normal span of life.

McGowan[13] gives an extended review in which he discusses some controversial points concerning the etiology of pernicious anemia and allied conditions, the nature of the changes in the marrow and the circulating blood, and the relation of subacute degeneration of the spinal cord to the disease.

(*b*) Influence of Solar Radiation: It had previously been claimed by Smith[14] that there was a significant relation between a relative lack of solar radiation and the mortality from pernicious anemia in the United States prior to the therapeutic use of liver. Apperly[15] warns that before accepting such a conclusion one should take into account that various additional factors may have determining effect. Among others, he names altitude, dust, various individual and racial differences, and possibly unknown conditions. The author considers that the relation between pernicious anemia and solar radiation might be more accurately shown by an attempted correlation of this disease with some other human malady which has a known relation to exposure to the sun's rays. With this in mind, the mortality from pernicious anemia before the modern treatment was introduced has been compared with the mortality from cancer of the skin in the various states of this country. A consideration of the collected data leads the author to conclude that the incidence of cancer of the skin (corrected for other causes than exposure to sunlight) has an inverse relation to that of pernicious anemia. This lends support to Smith's contention that the incidence of this variety of anemia is related inversely to the amount of solar radiation. The author reminds us that there is a relatively high incidence of pernicious anemia in blond and prematurely gray-haired persons, who are often of a eunuchoid type, and that the disease is often associated with diabetes. He emphasizes that argentaffin granules,

13. McGowan, J. P.: Pernicious Anaemia: Some Vital Considerations, Edinburgh M. J. **49**:568, 1942.

14. Smith, J. H.: The Relation Between Deficiency of Solar Radiation and Mortality Due to Pernicious Anemia in the United States, Am. J. M. Sc. **188**:200, 1934.

15. Apperly, F. L.: The Relation of Pernicious Anemia to Solar Radiation and Skin Cancer, Am. J. M. Sc. **203**:854, 1942.

para-aminobenzoic acid, melanin, insulin, estrogen and androgen are all composed chemically of benzene or aromatic rings, and he suggests that these substances are dependent for their formation on adequate production of dihydroxyphenylalanine through the agency of solar radiation.

(*c*) Studies on the Active Principle of Liver: Karrer[16] prepared a concentrated liver extract in an attempt to isolate the active principle and reports his studies on the composition and the characteristics of this principle. His method consists in extraction with 99 per cent ethyl alcohol followed by 50 per cent acetone. The latter is evaporated in vacuo, the proteins are precipitated with sulfosalicylic acid and the active principle is extracted with phenol. This impure preparation is then adsorbed on charcoal, washed with phenol five times and shaken with 75 per cent acetone. The active principle is found in the acetone-insoluble fraction. The pentose content is decreased, and repetition of the treatment with acetone results in a pentose-free substance. Further impurities are extracted with water-free pyridine. The material thus prepared was highly potent when tested clinically. Treatment with acetone of different concentrations or with ammonium sulfate did not fractionate it further. The preparations were not homogeneous, as was indicated by absorption spectrums, molecular weight analyses and determinations of the coefficients of dialysis through a membrane. Elementary analysis showed the following composition: carbon 45.6 per cent, hydrogen 6.7 per cent and nitrogen 14.6 per cent. The ninhydrin reaction was strongly positive, and the biuret test was weakly positive. The amino nitrogen content was 0.75 to 0.9 per cent; sulfur was present, but there was no pentose, protein or pterin. Following an eighteen hour hydrolysis with 20 per cent hydrochloric acid at 100 C., the amino nitrogen content increased to 9 per cent, and the original amino nitrogen content was doubled by trypsin and chymotrypsin at a p_H of 7.7 in thirty-eight hours. Pepsin in five-hundredth normal hydrochloric acid did not increase the amino nitrogen. The preparations were found to contain arginine and tyrosine but no phenylalanine, proline, hydroxyproline, glycine, tryptophane or histidine.

In 1935 Erdös,[17] now of the staff of the National Polytechnical Institute of Mexico, D. F., isolated from 1 Kg. of liver 5.8 Gm. of a yellowish brown powder as a silver salt. In this he discovered the presence of three free COOH groups and eighteen -CO-NH- groups and deduced a molecular weight of approximately 10,000. Four years later[18] he initiated new experiments, which form the basis for his present report. By acid aqueous extraction, treatment with barium hydroxide, concentration in a vacuum, addition of 99 per cent alcohol, filtration, reconcentration and precipitation with a solution of silver nitrate, he obtained a new silver salt having the following composition: carbon 67.50 per cent, hydrogen 6.40 per cent, oxygen 4.60 per cent, total nitrogen 14.40 per cent, amino nitrogen 1.40 per cent, sulfur 0.99 per cent, phosphorus 1.06 per cent, silver 5.04 per cent. One kilogram of liver yielded 2.09 Gm. of the substance, "which was extraordinarily active in clinical tests." For an approximate estimate of potency, the fractional precipitation with the alcohol test of Schales[19] and the author's own biologic test (based on the influence of the substance to be tested

16. Karrer, P.: Versuche zur Reinigung des Antiperniziosa-Faktors, Schweiz. med. Wchnschr. **71**:343, 1941.

17. Erdös, J.: Die Bewertung von Leber- und Magenpräparaten, Biochem. Ztschr. **277**:342, 1935.

18. Erdös, J.: The Chemical Composition of Liver Preparations, Science **96**:141, 1942.

19. Schales, O.: Einfaches Laboratoriumsverfahren zur vergleichenden Leberextraktprüfung, Klin. Wchnschr. **16**:277, 1937.

on anemia induced with phenylhydrazine) were employed. Further, he states that the results were confirmed by the clinical test of the reticulocyte response. It was concluded that for the present the following ideas can be entertained concerning the chemical structure of the active fraction of liver extract: It is an amino acid complex with three free COOH groups; it contains sulfur and phosphorus; it is soluble in water, acids and bases, precipitates with alcohol concentrations greater than 87 per cent and has a molecular weight of 6,000.

Treatment of Pernicious Anemia.—In regard to the treatment of macrocytic types of anemia, Castle [20] makes the following comments: First, that the conditions amenable to anti-pernicious-anemia therapy are true addisonian pernicious anemia, the macrocytic anemia of pregnancy and, in certain rare cases, nutritional macrocytic anemia due usually to intestinal disturbances. With the exceptions just noted, "all types of anemia fail entirely to respond to such preparations." He strongly advocates the use of preparations described in the United States Pharmacopeia or preparations accepted by the Council of the American Medical Association, the potency of which is defined in terms of official units. It is also emphasized that the most satisfactory form of anti-pernicious-anemia therapy is the intramuscular injection of a concentrated liver extract. The following reasons are given: The extract is from sixty to one hundred times as effective when administered parenterally as when given by mouth; a small volume, for instance 1 cc., containing 15 units, may be injected as infrequently as every two weeks to a month as a maintenance dose; the patient is less likely to discontinue the parenteral medication when the blood is normal; a certain unpredictable number of patients in severe relapse fail to respond adequately to oral medication; the neural manifestations are more amenable to this form of therapy. Although liver extracts contain various members of the vitamin B complex, it is Castle's opinion that these are nonessential to the success of the remission, and he considers their use in the treatment of pernicious anemia to be a waste of material. Although he admits that large amounts of whole or autolyzed yeast may cause improvement in patients with pernicious anemia, it is his belief that probably these agents act only indirectly through the power to form liver extract in the body. He concludes his remarks on therapy with the sound advice that the sole essential for maintaining continued and complete remission in pernicious anemia is the exhibition of sufficient amounts of active material by a single route at regular intervals. Finally, he questions the propriety of continuing to employ the adjective "pernicious" with reference to the disease, since the advances in therapy during the past fifteen years have almost deprived it of any meaning.

Strauss and his associates [21] have endeavored to clarify some of the problems incident to the use of liver extract in the treatment of patients with pernicious anemia. Their conclusions are based on observation of the blood levels of 80 patients who received liver extract in varying amounts and at different intervals over a period of five to nine years. As a result of their studies, they have adopted a uniform maintenance dose of 15 U.S.P. units of purified liver extract, injected every four weeks. In the eighteen months during which this plan has been in effect, no relapses have been encountered in the blood, the gastrointestinal system or the nervous system, either objective or subjective. They emphasize, however,

20. Castle, W. B.: Some Remarks on Therapy for Anemia, New England J. Med. **226**:903, 1942.

21. Strauss, M. B., and others: The Treatment of Pernicious Anemia: A Nine Year Study of Maintenance Requirements, with a Note on the Efficacy of Purified Liver Extracts in the Control of Neural Lesions, New England J. Med. **226**:1013, 1942.

that the maintenance requirements vary widely in different patients. From a practical standpoint, they do not consider a single red blood cell count, the Price-Jones measurement of the red blood cells or the estimation of the mean corpuscular volume as feasible types of information for the guidance of the physician. Their recommendations are as follows: (1) If the red blood cell count is persistently under 4,000,000 per cubic millimeter, 30 to 75 U.S.P. units of liver extract should be given weekly for two or three months, and if this augmented dosage results in higher blood values, one is justified in concluding that the previous dosage was inadequate; (2) if glossitis or unfavorable progression of the neural symptoms occurs, regardless of the high level of the red blood cell count, the treatment must be considered inadequate; (3) if the patient regains a feeling of better health when, unknown to him, he is receiving a larger amount of extract, the original treatment must be regarded as suboptimal. It is important from a practical standpoint to note that when in the 80 patients the interval between the intramuscular doses of 15 U. S. P. units was from one to four weeks, there was no change in the blood level and there was no neural relapse. This suggests strongly that the anemia of the average patient can be controlled on such a dosage. Nevertheless, the authors state clearly that probably certain patients require more liver extract than this amount, particularly in the presence of infection or of severe damage to vital organs.

Della Vida and Dyke[22] comment on their experience in the treatment of patients for pernicious anemia by intramuscular injections of liver extract, stating that only at the beginning of therapy are weekly doses given; thereafter, the great majority of patients are maintained satisfactorily on doses given once every two or three months. They administer a dose of 4 to 6 cc. of fully potent liver extract. Widely varying dosages of liver extract are used in the treatment of pernicious anemia, owing partly to custom and partly to the employment of extracts of low potency, according to these authors. In an effort to establish new criteria of potency, a series of 125 cases of pernicious anemia were reviewed, and the relation between the red blood cell count before, and its increase during, the first two weeks of parenteral injection of liver extracts has been expressed by mathematical equations. It was concluded that in a majority of the cases the response exceeded that anticipated from previously published formulas and that the red blood cell increase was more reliable in assaying the potency of liver extracts than the reticulocyte response. The formula $I\ 0.93 - 0.214\ Eo$ (in which I is the average weekly increase in red cells during the first two weeks of treatment and Eo is the red cell count before treatment) has been found to express a satisfactory response to treatment and is proposed as the standard equation for the assay of the potency of liver extracts. Following this article is a note by Dyke on the dosage of liver extract, in which he refers to the action of the Anti-Anemia Preparations Advisory Board of the United States Pharmacopeia and states that their units are based on the red blood cell count and the reticulocyte response. In his opinion the assay should be based entirely on the increase in the red blood cell count. Furthermore, he believes that units should not be utilized, but the actual amount of liver necessary to produce a red cell response according to an accepted formula. We consider, after a thorough trial of the present U.S.P. unit system, that it serves its purpose satisfactorily, and we see no objection to evaluating the potency of any given sample of liver extract by utilizing both the red blood cell and the reticulocyte increase.

22. Della Vida, B. L., and Dyke, S. C.: Maximal Response to Liver Therapy in Pernicious Anemia, with a Note on Dosage, Lancet **2**:275, 1942.

Askey [23] advocates, as the routine treatment for pernicious anemia, an initial intramuscular injection of a massive dose of liver extract followed by monthly injection of doses sufficient to replenish the utilized material. He assumes that a normal human liver, weighing 1,500 Gm., stores approximately 125 to 225 U.S.P. units and that this is apparently exhausted when the patient has severe anemia. This amount plus that needed by other body tissues in relapse should represent several hundred units. The procedure now used tentatively at the Los Angeles General Hospital is as follows: One cubic centimeter of a concentrated liver extract, containing 15 U.S.P. units, is administered intramuscularly. If there is no untoward reaction, the following day 9 cc. is injected. This brings the total dose to 150 units. Thereafter, at monthly intervals a dose of liver extract containing 30 units is given. Vitamin B is not prescribed, as it is thought that the vitamin needs are supplied by the liver extract and by a general diet. If the gastrointestinal symptoms persist after the blood returns to normal, dilute hydrochloric acid is given, but this has rarely been found necessary. Occasionally, in conjunction with the liver therapy, medicinal iron is administered.

A symposium on the treatment of pernicious anemia is given [24] by a group of the leading internists of Germany, including Heilmeyer, of Jena, Nonnenbruch, of Frankfort on the Main, Hoff, of Graz, Schilling, of Rostock, Bingold, of Nuremberg, and Buding, of Berlin. As their opinions concerning the various aspects of therapy are much in accord, no attempt will be made to record individual statements. In general, it was agreed that the intramuscular injection of liver extract is the best form of therapy. Usually a preparation corresponding to a purified solution of liver U.S.P. was given in doses of 2 to 4 cc. every two to four weeks. Some patients were treated as often as once a week; others, especially those who did not return for observation at regulation intervals, were given "depot injections"; i. e., 5 to 10 cc. of a potent liver extract was injected intramuscularly every four to six weeks. The fact that no test animals are available makes the greatly desired standardization of liver preparations for parenteral use impossible, and consequently, as one contributor said, "the patient himself must be the test object." In no instance was a patient with uncomplicated pernicious anemia found to be refractory to potent therapy. It was said, however, that vitamin deficiency might inhibit the anticipated response. The maintenance dose of liver extract was considered to vary greatly with different patients, just as does the dose of insulin for patients with diabetes mellitus. One patient who stopped therapy had no relapse for a year and a half. That is unusual, but the example serves to illustrate that the maintenance dose is not the same for all patients. It was generally agreed that an increased amount of therapy is required by older patients and by those in whom infection develops. The injection of an excess of liver extract is not regarded as a waste, for any amount over immediate demand is stored in the body and utilized when needed. The results in the subacute combined degeneration of the cord are not as striking as in the anemia, but in all instances the process is arrested, and in some a remarkable improvement occurs. Usually, large doses of liver extract are injected, in combination with parenteral injections of vitamin B_1. One contributor advised that 4 cc. be injected intramuscularly daily for weeks, in combination with parenteral injection of vitamin B_1. There was uniform agreement that no case of the achrestic anemia of Wilkinson

23. Askey, J. M.: Pernicious Anemia: Adequate Versus Optimum Treatment, California & West. Med. **56**:72, 1942.

24. Heilmeyer, L.; Nomrebrach, W., and Fox, F.: Die Bioerkmaszigste Art der Behandlung der perniziösen Anämie, Med. Klin. **38**:169, 1942.

had been observed. In most instances, desiccated stomach therapy had not been used in a sufficient number of patients to enable the observer to express an opinion as to its efficacy. Dilute hydrochloric acid was thought to be of little value, and arsenic, congo red and choline were not considered helpful in the treatment of this disease. It is of interest that all of the contributors to the symposium favored the administration of iron, especially in the early stages of remission, when the red blood cells increase more rapidly in number than does the hemoglobin content of the circulating blood. Consequently, at this stage of therapy the color index commonly falls below 1. There may be a greater need for supplemental iron in Germany because of dietary deficiency.

Fullerton [25] assigns the responsibility for inadequate maintenance therapy in cases of pernicious anemia to those practitioners who are ignorant of the elementary therapeutic principles employed in treating the disease. According to him, maintenance treatment is frequently reduced to grossly insufficient dosages, or patients may even be advised that therapy is unnecessary as long as they feel well. He warns that such management may lead to progression of subacute combined degeneration of the spinal cord. He very properly advises his patients that treatment must continue throughout the remainder of life. He concludes by stating that if all practitioners realized the importance of adequate maintenance therapy the death rate from pernicious anemia would show a sharp decline. He emphasizes, furthermore, that treatment should be controlled by examinations of the blood.

Accurate diagnosis of blood disorders, based on the changes in the blood and on the clinical features, is emphasized by Vandersluis [26] as a prelude to the inauguration of therapy. He states that in making the diagnosis of pernicious anemia one should keep in mind macrocytosis, leukopenia with relative lymphocytosis, and megaloblastic hyperplasia of the marrow. The clinching proof of the identity of the disease is the reticulocyte response to liver therapy. The author is aware that the hematologic changes seen in pernicious anemia may occur in other conditions and accordingly reminds the reader that the diagnosis depends on the clinical features of the disease as well as on the laboratory findings.

Dyke [27] comments on the soundness of the order of the British government that only liver preparations suitable for injection will be made in England henceforth. He points out that the oral mode of administration is wasteful and that, even though preparations will be available for intramuscular injection, they should be administered judiciously. By this is meant that they should be given only to those patients whose disease has been established definitely as pernicious anemia by the utilization of all modern diagnostic methods, and to such patients in the minimum adequate dosage. Furthermore, a plea is made to establish in England a standard statement of the potency of the type of liver extract hidden under the trade name, especially now that a brand familiar to the physician may often be temporarily unobtainable.

Dyke, Della Vida and Delikat [28] have observed the tendency of patients with pernicious anemia to relapse during the spring of the year and attribute this to a deficiency of vitamin C. This conclusion is based on the successful treatment of

25. Fullerton, H. W.: Pernicious Anaemia, Brit. M. J. **2**:291, 1942.
26. Vandersluis, C.: Hematology of Pernicious Anemia, Minnesota Med. **25**:36, 1942.
27. Dyke, S. C.: Husbanding of Liver Extracts, Lancet **1**:185, 1942.
28. Dyke, S. C.; Della Vida, B. L., and Delikat, E.: Vitamin-C Deficiency in "Irresponsive" Pernicious Anaemia, Lancet **2**:278, 1942.

patients by the administration of vitamin C and continuation of exactly the same dosage of liver extract. The authors contend that the diet of the general population of England under war conditions is known to be deficient in this vitamin. According to them, even with ample dosage of liver extract, hemopoiesis cannot be returned to normal in the face of a deficiency of vitamin C.

Cole [29] reports the case of a 3 week old infant who had pronounced macrocytic anemia with a red blood cell count of 2,650,000 per cubic millimeter and a hemoglobin value of 54 per cent. Normoblasts, megaloblasts and primary erythroblasts were present in the peripheral blood. Following a single intramuscular injection of liver extract, there was a reticulocyte rise to a maximum of 22.5 per cent on the seventh day after treatment, and eventually a complete hematologic and clinical recovery. It is suggested that the child began life with a deficiency of the anti-pernicious-anemia principle and that treatment with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) and sulfanilamide for a pulmonary infection may have been contributing factors.

Nutritional macrocytic anemia which responded to liver extract in an infant 4 months old is reported by Fouts and Garber.[30] The infant had suffered from vomiting, had refused to take food and had lost weight. It may be of importance that the mother during gestation had eaten no meat on account of previous toxemia of pregnancy. The red blood cell count was 910,000 per cubic millimeter. There was no response to iron, brewers' yeast and various preparations of the vitamin B complex. The mean corpuscular volume was 92 cubic microns. It was assumed that the macrocytosis was more pronounced prior to blood transfusions. Following the intramuscular injection of 0.25 U.S.P. unit of purified liver extract daily, the reticulocytes rose to a peak of 26.8 per cent. After three months of liver extract therapy, the child had gained approximately 5 pounds (2,268 Gm.) in body weight ,and the blood was normal. According to the authors, this condition is not common. It most frequently appears after an infection of the upper respiratory tract followed by vomiting or diarrhea or both. These patients are notably malnourished and fail to gain weight on change of formulas. Apparently, the anemia in this patient was due to inadequacy of the amount of extrinsic factor in the diet plus deficiency of protein intake in the mother during gestation.

Goldstein [31] by a search through the literature and by personal communications has investigated the question whether polycythemia may be induced by liver treatment in patients with pernicious anemia. The evidence accumulated was much against this possibility. The reply of W. B. Castle, of Boston, is the most complete answer to the inquiry, and it is quoted in full:

> The only suspicion of erythrocytosis in connection with the therapy of pernicious anemia which I have observed is the occasional patient who, before the hemoglobin reaches a normal value, may have transiently a red blood cell count of 5½ to 6 million. I take it that this is not, however, polycythemia because of the normal or subnormal hemoglobin values.
>
> I was very much interested in Birnies' report and consider that his patient represented a chance association between whatever factors make for polycythemia vera and whatever factors make for pernicious anemia. The remission produced in the pernicious anemia by adequate liver therapy allowed the polycythemia to express itself.
>
> So far as I know, it is impossible to raise the red count or the hemoglobin above normal in normal individuals by liver extract or iron therapy, so that I consider it unlikely that the

29. Cole, L.: Hyperchromic Anaemia in an Infant: Response to Liver Extract, Lancet **2**:759, 1941.

30. Fouts, P. J., and Garber, E.: Nutritional Anemia in an Infant Responding to Purified Liver Extract, Am. J. Dis. Child. **64**:270 (Aug.) 1942.

31. Goldstein, H. I.: Pernicious Anemia Alternating with Polycythemia Polyglobulia. Rev. Gastroenterol. **9**:406, 1942.

status of the gastric secretion bears any relationship to the development of polycythemia, with the single exception that so far as the blood values are concerned, pernicious anemia in relapse and polycythemia cannot coexist simultaneously.

George R. Minot adds his comment, as follows:

I do not think that patients with pernicious anemia will develop polycythemia with a return of free hydrochloric acid in the gastric contents.

We wish to add that we are in entire accord with the statements of both Castle and Minot.

Ferrary,[32] in a study of the erythremic response to liver therapy, presents the case of a 64 year old woman with pernicious anemia complicated with diabetes mellitus in whom there developed an excessive increase of red blood cells and hemoglobin after intramuscular administration of liver extract. This patient had been treated when in relapse, and her blood promptly returned to normal. After a period of approximately a year, however, during which time she had been given liver extract in doses of 10 U. S. P. units weekly, she was found to have a hemoglobin level of 131 per cent and an erythrocyte count of 10,650,000 per cubic millimeter. After the therapy had been omitted for about one month, the hemoglobin value was found to be 120 per cent and the erythrocyte count 6,250,000. Two weeks later the therapy was resumed, with doses of 10 units being given every three weeks, and after an interval of approximately eight months the hemoglobin was 100 per cent and the red blood cell count 5,050,000. According to the author, there are three possible explanations of the erythremoid reaction: (1) The administration of liver extract may have been continued through a period of spontaneous remission; (2) the patient's hemopoietic response may have been overstimulated by a relative overdosage of liver extract; (3) perhaps, associated diabetes produced the condition by dehydration and hemoconcentration. It is considered that, of these possibilities, the first is the most likely explanation, and hence it is his view that the erythremoid blood picture could not be reproduced without the assistance of a spontaneous remission. This case in our opinion is unique, as a similar one has not been observed by us in approximately fifteen years during which many patients have been treated, some with exceedingly large doses. Certainly, from a practical standpoint there is no danger of overtreatment; in fact, the great difficulty in the therapy of the disease is to guard against undertreatment. Whatever may have been the cause of the increased red blood cell count, in our opinion it probably was not related directly to liver extract therapy.

Bone Marrow in Pernicious Anemia.—Davidson and his associates[33] have made a study of the changes observed in films prepared from sternal marrow in cases of pernicious anemia before, and at various short intervals after, the initiation of liver therapy. To obtain a working classification, they divided all erythroblastic marrow cells in Romanowsky-stained films into four types, differentiated chiefly by nuclear structure. For the detailed characteristics of the four groups, reference should be made to the original article. They observed that within six to ten hours after the initial injection of liver extract there is a reduction in the mean size of the predominant cells, accompanied by a striking alteration in the character of the nucleus. In other words, type II increases in frequency at the expense of type I, which is the most primitive type. After thirty-two to seventy-

32. Ferrary, P. B.: Erythremic Response to Liver Therapy in Treatment of Pernicious Anemia, J. M. Soc. New Jersey **39**:19, 1942.

33. Davidson, L. S. P.; Davis, L. J., and Innes, J.: The Effect of Liver Therapy on Erythropoiesis as Observed by Serial Sternal Punctures in Twelve Cases of Pernicious Anaemia, Quart. J. Med. **11**:19, 1942.

two hours the change is still more pronounced, as the picture is dominated by the even more mature type III cells. In other words, the megaloblastic picture becomes normoblastic. The authors are inclined to believe that the mechanism underlying the widespread cellular change is a direct physicochemical process due to the action of the liver extract, rather than cellular mitosis. They believe also that the rapidity of the change from a megaloblastic to a normoblastic marrow supports the view that normoblasts can be derived directly from megaloblasts. Furthermore, they consider that they have collected evidence from a study of the sternal marrow in cases of severe untreated iron-deficiency anemia and hemolytic anemia which suggests that under severe and prolonged strain the normoblastic may revert toward the megaloblastic blood picture. If this occurs, according to the authors, it is additional evidence that megaloblasts and normoblasts belong to one developmental series.

In a letter to the editor of the *Lancet*, Davidson, Davis and Innes [34] urge that the clinician who is not engaged in research in hematology rely on intelligent studies of the peripheral blood as his diagnostic mainstay in dealing with various diseases of the blood rather than on a study of the sternal marrow. They contend that sternal puncture is necessary only in the occasional cases in which anemia fails to respond to adequate doses of liver extract or iron or in which purpura or leukopenia is an unexpected presenting feature. Furthermore, in such cases a helpful interpretation of the marrow can be given only by those who have had considerable experience in such work. It is emphasized also that the diagnosis of pernicious anemia and of other disorders of the blood is not made on the presence or the absence of any particular cell type, such as the megaloblast, but on the frequency distribution of the various cells constituting the marrow. In the same issue of the *Lancet* is a communication by Murray,[35] who likewise states that pernicious anemia can be, and still is, diagnosed by physicians who recognize the clinical picture and call on the pathologist to confirm it by an interpretation of the blood picture. He infers, and very properly in our minds, that a complete examination of the blood, with a halometer reading, followed by a reticulocyte count made after an adequate dose of a potent liver extract can confirm the diagnosis in most instances.

In an editorial review entitled "The Clinician and the Megaloblast" [36] it is stated that the presence of the megaloblast in the blood and the marrow indicates a reversion to the embryonic type of formation of red blood cells. To the clinician, from the time of Ehrlich the megaloblast in the blood stream meant strong support for the diagnosis of pernicious anemia. After a lapse of some years, in 1927, the importance of the megaloblast in this disorder received renewed emphasis from the work of Peabody. This investigator observed that liver therapy caused a megaloblastic marrow to change rapidly into a marrow in which normoblasts and then mature erythrocytes predominated. His conclusion assumed logically that liver extract hastened the maturation of the red blood cells in the marrow. With the widespread use of the sternal puncture, a large amount of information has accumulated about this problem. It is now thought that there are two interchangeable series of erythroblasts—megaloblasts and normoblasts—which are derived from a common basophilic stem cell (proerythroblast). It is a common belief that the anemia associated with megaloblastic hyperplasia will respond favor-

34. Davidson, L. S. P.; Davis, L. J., and Innes, J.: Diagnosis of Pernicious Anaemia, Lancet **1**:428, 1942.

35. Murray, D. S.: Diagnosis of Pernicious Anaemia, Lancet **1**:428, 1942.

36. The Clinician and the Megaloblast, editorial, Lancet **1**:358, 1942.

ably to liver therapy whereas the anemia which is not associated with megaloblasts is refractory to this therapeutic agent. Israëls[37] has recently identified seven different types of erythroblasts, whereas Davidson and his associates divide these cells into four groups, but it is pointed out that perhaps it is sufficient for the clinician to know whether the marrow is predominantly megaloblastic or predominantly normoblastic or mixed in character.

Israëls[37] in reply to several letters of criticism with regard to the diagnosis of pernicious anemia and with special reference to the clinical study of the marrow, emphasizes that in hematology, as in other fields of medicine, the diagnosis depends on a consideration of the whole picture as presented by all of the information available. He considers that the most important information obtained from the marrow with reference to the diagnosis of anemia is whether the marrow is hypoplastic, hyperplastic or about normal and whether it is megaloblastic or normoblastic. According to him, megaloblastic marrow occurs in pernicious anemia, in the refractory achrestic anemia and in certain types of nutritional anemia, such as that accompanying sprue. "Apart from these," he states, "in my extensive experience, normoblastic marrow is always present." He considers, therefore, that the total change in the marrow is of diagnostic importance. He does sternal puncture commonly, according to the following indications: any doubt about the diagnosis, such as a history of failure of liver therapy; unusual age or exceptional clinical signs or symptoms; grave anemia with an equivocal blood picture, and, finally, any case the subject of research about which the fullest information is desirable.

Wilson[38] gives a most comprehensive review of present knowledge of the marrow in anemia, including the historic aspects, and devotes considerable discussion to the changes which occur in pernicious anemia. He has described serial examinations of marrow in cases of pernicious anemia, the specimens being obtained during relapse, before treatment, in remission and again in an early stage of relapse. It is his conclusion that, following liver therapy, there is ripening of the abnormal megaloblasts, without the development of further megaloblasts. He is also of the opinion that there is initial temporary stimulation and then, later, lesser but more prolonged stimulation of the definitive normoblastic cells. He does not regard the abnormal granular cells present in pernicious anemia or the megaloblastic cells as representing a reversion to embryonic erythropoiesis. He concludes that a reappearance of the megaloblasts during a relapse is due to megaloblasts which have persisted in the marrow in numbers too small to be detected in aspirated material. The megakaryocytes are reduced in number in the marrow of patients with pernicious anemia who are untreated either during relapse or during remission. His observations of the marrow of patients with subacute combined degeneration of the spinal cord in whom there was no anemia indicated that the only abnormality present was the "giant stab forms." He suggests that possibly these may represent the initial change in the marrow in patients with pernicious anemia.

Dacie,[39] in discussing the diagnosis of pernicious anemia by means of sternal puncture, states that it is exceedingly difficult to distinguish between megaloblasts and primary erythroblasts. He believes that they merge imperceptibly into each other. However, he finds the following working hypothesis helpful: Megaloblasts are considered to be primary erythroblasts of varying maturity which, because

37. Israëls, M. C. G.: Diagnosis of Pernicious Anaemia, Lancet **1**:487, 1942.
38. Wilson, T. E.: Bone Marrow in Anaemia, M. J. Australia **1**:513, 1942.
39. Dacie, J. V.: Diagnosis of Pernicious Anaemia, Lancet **1**:520, 1942.

of retarded development, may receive hemoglobin at an unusually early age and thereby become polychromatic or orthochromatic. This quantitative change may be observed in all degrees of intensity according to the rates at which the cells develop and the stages of development at which the hold-up occurs. In patients with pernicious anemia in severe relapse, the maturation of the hemocytoblasts and of the early primary erythroblasts is arrested, and many of the nucleated cells containing hemoglobin are large and have relatively immature nuclei. In certain other obscure types of anemia, the maturation is delayed at a later stage, and consequently the megaloblasts, if present, are smaller and more mature.

In an abstract of a paper presented before the New England Pathological Society, Williams [40] reports on histologic studies of megaloblastic marrow which were made for the purpose of determining the criteria by which the megaloblastic can be distinguished from other reactions of the marrow. The material studied consisted of 10 specimens of sternal marrow obtained in 9 cases of pernicious anemia in relapse. It was concluded that the megaloblastic hyperplasia seen in sections of sternal marrow from patients with a red blood cell count of 2,000,000 per cubic millimeter or less presents the following highly characteristic picture: a pronounced increase in cellularity; the presence of large immature basophilic cells, which are clumped together in islands and sinuous columns forming a lacelike network throughout the marrow; the absence of definite islands of mature and moderately mature erythropoiesis; the occurrence of frequent foci of granulopoiesis composed almost exclusively of mature neutrophilic myelocytes, metamyelocytes and polymorphonuclear leukocytes; a striking decrease in the number of megakaryocytes.

It is believed by Limarzi and Levinson [41] that the amitotic and multipolar erythropoiesis which they observed in aspirated specimens of marrow from a patient dying of a rare condition may explain the rapid conversion of megaloblastic to normoblastic marrow following the administration of liver extract to patients with pernicious anemia. They also conclude that evidence is available to support the belief that two different types of erythropoiesis occur simultaneously in the bone marrow of patients with pernicious anemia: the normal bipolar type of mitosis and maturation, and the abnormal form described. They consider that liver therapy acts on the pathologic tissue and possibly results in multipolar mitosis and the development of multinucleated erythroid cells. This, they believe, may explain in part the rapid conversion (not maturation) of megaloblastic to normoblastic marrow within twenty-four hours in some patients with pernicious anemia.

Changes in the Nervous System in Pernicious Anemia.—The possibility that further light might be thrown on the cause and the nature of subacute combined degeneration of the spinal cord in man by a study of a primary degenerative demyelinating lesion of the spinal cord of the monkey is considered by Hamerton.[42] He studied such lesions as they occurred spontaneously in monkeys of the London Zoo over a period of seven years. Macrocytic anemia was observed in 1 animal, and lymphatic leukemia in another. Achlorhydria was present in the 3 animals studied by gastric analysis. All the monkeys with these lesions showed intention

40. Williams, R. J.: The Histology of the Megaloblastic Hyperplasia of the Bone Marrow, New England J. Med. **227**:938, 1942.

41. Limarzi, L. R., and Levinson, S. A.: Undescribed Type of Erythropoiesis Observed in Human Sternal Marrow and Its Relationship to the Mechanism of Megaloblast-Normoblast Maturation, Proc. Inst. Med. Chicago **14**:232, 1942.

42. Hamerton, A. E.: Primary Degeneration of the Spinal Cord in Monkeys: A Study in Comparative Pathology, Brain **65**:193, 1942.

tremor of the hands, spastic paraplegia affecting the hindlegs, wobbling, rapidly increasing ataxia with progressive diminution of power and, finally, complete flaccid paralysis of the hindlimbs and tail. The limb reflexes, at first increased, were absent in the final stages of the disease. Loss of sensation was a late symptom in most cases. The histologic picture of primary degeneration of the spinal cord in monkeys appears to be indistinguishable in its main features from that of subacute combined degeneration in man. The primary lesion is not sclerosis but true softening with fatty degeneration of the myelin sheaths and subsequent disappearance of the axis cylinders, without any inflammatory gliosis. The histologic resemblance, however, is no criterion for the belief that they are identical diseases. Much more comparative study must be done before the identity of the two conditions can be established. The possibility is mentioned that the disorder may arise from a vitamin deficiency. Suggestive evidence was obtained that a product equivalent to a purified solution of liver U. S. P. containing vitamin A, B_2 and B_6 might be of real benefit in the condition.

The case of a man, aged 24, with pernicious anemia and subacute combined degeneration of the spinal cord is presented and discussed by Ranson and Reback.[43] The neurologic condition was noted at a relatively early age, the response to therapy was remarkably good, and there were some interesting hereditary features. The earliest manifestations of pernicious anemia appeared at the age of 22 years, and those of subacute combined degeneration of the cord, at 24 years. The latter developed despite oral liver therapy, which did not keep the blood entirely within normal limits but in the vicinity of 4,000,000 red blood cells per cubic millimeter, at least for part of the time. When first observed by the authors, the young man was moribund, completely paralyzed in both legs and psychotic. After massive doses of liver extract and thiamine had been given parenterally, followed by massage, passive and active exercises and, as soon as feasible, reeducational walking exercises, he improved remarkably. Four months after his discharge from the hospital, he returned to work, discarded his cane and could walk as far as 14 blocks without difficulty. Sixteen months after discharge, his gait appeared to be normal, but it should be noted that there was persistence of hyperreflexia and of pathologic reflexes and that the vibratory and positional sense of the legs was still impaired. The authors suggest that the remarkable improvement was due to the parenteral administration of large amounts of liver extract and thiamine and to the early initiation and vigorous continuation of physical therapy and reeducational measures. The continued improvement they attribute in part to the maintenance of the patient's red blood cell count above 5,000,000 cells per cubic millimeter by intramuscular injection of appropriate doses of liver extract. We are in accord with these statements but would like to emphasize that one other aspect of this patient's illness was of favorable significance with reference to the changes in the spinal cord, namely that, although he had experienced the symptoms of pernicious anemia for about two years, the changes in the spinal cord had been present for only about four months. Experience has shown that the duration of the neurologic manifestations bears a greater relation than does the extent of the changes to the degree of subsequent improvement. Another interesting phase of subacute combined degeneration of the spinal cord is emphasized by the aforenamed authors, namely, the hereditary tendency, which undoubtedly plays an important role in its etiology. They refer to previous publications by various authors who have reported the occurrence of subacute combined degeneration in

43. Ranson, S. W., Jr., and Reback, S.: A Case of Subacute Combined Degeneration of the Spinal Cord with Interesting Hereditary Features, Ann. Int. Med. **17**:738, 1942.

more than one person of the same family. The mother and a maternal uncle of their patient both had pernicious anemia with subacute combined degeneration of the spinal cord. The data, which the authors admit are "scanty," suggest the transmission of the disease as a mendelian recessive character.

Bleecker [44] reports the case of a patient with a severe involvement of the central nervous system characteristic of subacute combined degeneration of the spinal cord but with a normal blood count, and emphasizes that patients of this type can be benefited with appropriate liver therapy. He states that severe neurologic manifestations do not mean necessarily that permanent damage has been done to the cells of the spinal cord and that function may not return to normal with the proper therapy. He suggests treatment with liver extract in large doses, supplemented by the "gastric factor" (desiccated hog stomach in the case reported), dilute hydrochloric acid, adequate diet and thiamine hydrochloride. He believes that a decrease in the mean corpuscular volume and the mean corpuscular hemoglobin concentration is of favorable prognostic significance.

In relation to subacute combined degeneration of the spinal cord it is possibly of interest that degeneration of sensory neurons involving the peripheral nerves, the posterior root ganglions, the posterior roots and the posterior funiculi of the spinal cord can be produced in pigs by means of a diet deficient in calcium pantothenate or pyridoxine. It is concluded by Wintrobe and his associates [45] that pyridoxine and pantothenic acid are necessary in maintaining the integrity of the nervous system. These neural changes developed in animals when the diets contained adequate amounts of thiamine, riboflavin, nicotinic acid, wheat germ oil and cod liver oil, as well as sufficient protein, carbohydrate, fat and minerals. We are of the opinion that a deficiency of pyridoxine or of pantothenic acid, or a disturbance in their metabolism, may account for the lesions of subacute combined degeneration but that the possibility is still a matter for investigation.

It is considered by Meyer, Burton and Sturgis [46] that neural changes in pernicious anemia arise from a deficiency of some unidentified factor other than that required for hemopoiesis. Since achlorhydria is invariably present in patients with pernicious anemia, the possibility must be considered that this condition results from decreased absorption of certain vitamins. Following the report of Street, Cowgill and Zimmerman [47] that a deficiency of riboflavin caused degenerative changes in the peripheral nerves and in the posterior columns of the spinal cord in dogs, Meyer and his associates attempted to determine whether patients with pernicious anemia had diminished ability to absorb riboflavin by measuring the daily urinary excretion according to the method of Snell and Strong.[48] The subjects of the study were 12 hospital patients with pernicious anemia and 12 healthy students, both groups on unrestricted diets, and no indication was found that achlorhydria impaired the absorption of this vitamin. When 5 Gm. of riboflavin was added to the diet of each group, no tendency toward a lesser excretion of this substance was observed in the patients with pernicious anemia. These results resemble those obtained in a similar study of the excretion of pantothenic acid reported by Meyer, Burton and

44. Bleecker, P. B.: Preanemic Subacute Combined Degeneration of the Spinal Cord: A Case Report, Mississippi Doctor **20**:83, 1942.

45. Wintrobe, M. M., and others: Sensory Neuron Degeneration in Pigs: Protection Afforded by Calcium Pantothenate and Pyridoxine, J. Nutrition **24**:345, 1942.

46. Meyer, C. E.; Burton, I. F., and Sturgis, C. C.: Riboflavin Absorption in Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **50**:251, 1942.

47. Street, H. R.; Cowgill, G. R., and Zimmerman, H. M.: Further Observations of Riboflavin Deficiency in Dog, J. Nutrition **22**:7, 1941.

48. Snell, E. E., and Strong, F. M.: The Microbiological Assay of Riboflavin, Indust. & Engin. Chem. (Anal. Ed.) **11**:346, 1939.

Sturgis.[49] This substance, like thiamine, is alkali labile and hence might be destroyed in the intestinal tract of patients with achlorhydria, so that a deficiency would be caused. In a study of 7 patients with pernicious anemia and a like number of healthy controls it was found that the daily excretion of the substance when determined by the method of Snell, Pennington and Williams [50] both before and after the administration of 100 mg. of its calcium salt was slightly but probably not significantly less than that of healthy persons studied in the same manner. This indicates that there is no impairment of its absorption in patients with pernicious anemia. Phillips and Engel [51] report the occurrence of a disease of the spinal cord in chicks receiving a diet deficient in pantothenic acid. The possibility cannot be excluded that the absence of hydrochloric acid may make the riboflavin and the pantothenic acid in food less available for absorption, and therefore the degenerative changes of the nervous system in patients with pernicious anemia may result from a conditioned avitaminosis present over a long period.

Pernicious Anemia and Carcinoma of the Stomach.—Bronstein [52] adds another to the group of cases of pernicious anemia in which after a variable number of years carcinoma of the stomach has developed. There is certainly no incompatibility between the two diseases. In fact, the question has been asked, Does not the atrophic gastritis of pernicious anemia predispose to the rise of a neoplasm in the gastric mucosa? His patient was a Greek of 45 years who had all of the classic manifestations of true addisonian pernicious anemia, which responded satisfactorily to parenteral injection of liver extract. After four and one-half years his weight decreased from 127 to 112 pounds (57.5 to 51 Kg.). This led to a roentgen examination of the gastrointestinal tract, which disclosed a neoplasm of the middle portion of the stomach, on the side of the greater curvature. At necropsy a fungating tumor (adenocarcinoma) was found involving the fundus of the stomach. At the time the cancer developed, there was a change in the character of the blood picture, as was to be expected. The color index became less than 1.0; the size of the erythrocytes decreased, as did the mean corpuscular hemoglobin concentration. The author discusses the association of pernicious anemia and carcinoma of the stomach and suggests that patients with the former disease should be studied with great care if there is a change in the character of the anemia. The reviewers consider that it is logical to observe an increasing number of patients with the two diseases since, with the modern treatment, those having pernicious anemia now survive to an age when cancer is common. The question is not yet answered as to whether carcinoma of the stomach is more likely to develop in patients with pernicious anemia than in other persons of the same age group, but this is a possibility.

Doehring and Eusterman [53] review the literature dealing with the association of pernicious anemia and carcinoma of the stomach in the same patient, and add a group of cases in which this has been observed at the Mayo Clinic. During the period between 1935 and 1939 approximately 1,014 patients with pernicious

49. Meyer, C. E.; Burton, I. F., and Sturgis, C. C.: Pantothenic Acid Absorption in Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **49**:363, 1942.

50. Snell, E. E.; Pennington, D., and Williams, R. J.: Effect of Diet on Pantothenic Acid Content of Chick Tissues, J. Biol. Chem. **133**:559, 1940.

51. Phillips, P. H., and Engel, R. W.: Some Histopathologic Observations on Chicks Deficient in Chick Antidermatitis Factor or Pantothenic Acid, J. Nutrition **18**:227, 1939.

52. Bronstein, L. H.: Carcinoma of the Stomach Developing in Pernicious Anemia, J. Lab. & Clin. Med. **28**:44, 1942.

53. Doehring, P. C., and Eusterman, G. B.: Association of Pernicious Anemia and Carcinoma of the Stomach, Arch. Surg. **45**:554 (Oct.) 1942.

anemia were observed at this clinic, and 17 had carcinoma of the stomach, which gives an incidence of 1.7 per cent. They state that the number of patients in whom these diseases are combined is increasing but that it is difficult to say whether this is due to the increased length of life of patients with pernicious anemia or to some change in the stomach peculiar to addisonian anemia which makes these patients more likely to have new growths of that organ. It is their opinion that lengthened period of survival accounts in part for the situation. On the other hand, from their calculations they estimate that the incidence of carcinoma of the stomach in patients with pernicious anemia at the clinic is greater than the frequency which one would expect in the same age group in the population at large. In 10 of the 17 cases in which pathologic material was obtained, the neoplasm was found to be adenocarcinoma with a varying degree of malignancy. They also observed among 1,014 patients with pernicious anemia 4 with benign polyps, which gives an incidence of 0.39 per cent. The symptoms of pernicious anemia appeared in this group of 17 patients at the average age of 54.5 years, and those of carcinoma of the stomach at 63.2 years. The authors speculate concerning the etiologic relation between the two diseases and conclude that, although the evidence is incomplete, there are grounds for suspecting that persons with pernicious anemia are slightly more likely than other persons to have gastric carcinoma. They also report concerning the relation of anemia to gastric resection that in a series of 474 cases of gastric resection for cancer, in 14 of which the operation was total gastrectomy, pernicious anemia developed in not 1 case.

Miscellaneous Observations Concerning Pernicious Anemia.—In 1937 Snapper, Groen, Hunter and Witts [54] reported a series of cases in which pituitary disease was associated with achlorhydria and anemia, usually of the addisonian type. Witts [55] now reports 2 more cases, and from what he has learned of others from colleagues he is convinced that the occurrence of these two diseases in the same patient is more than a coincidence. In his opinion, the association of pernicious anemia with hyperthyroidism, with pregnancy and with pituitary disease suggests that there is a defect in some hormonal element or mechanism which may lead to degeneration of the cells in the stomach responsible for the secretion of the intrinsic factor. In his opinion, the combination of this type of anemia with pituitary disease is another example of the precocious senile changes to which the patient with such disease is liable.

The case of a 41 year old white woman with pernicious anemia and lesions reported on roentgen examination of the chest as bilateral pulmonary tuberculosis of undetermined activity is reported by Skavlem and Storey.[56] The association of this blood disorder with pulmonary lesions that possibly were tuberculous caused them to review the literature dealing with the occurrence of these two conditions in the same patient. From the literature they conclude that most writers on this subject agree that the two diseases are rarely seen concurrently, and some observers believe that there is antagonism between them. They state that only two authors hold a contrary view, one on grounds not wholly tenable. Their own patient was apparently not suffering from active tuberculosis, as indicated by sub-

54. Snapper, I.; Groen, J.; Hunter, D., and Witts, L. J.: Achlorhydria, Anaemia and Subacute Combined Degeneration in Pituitary and Gonadal Insufficiency, Quart. J. Med. **6**: 195, 1937.

55. Witts, L. J.: Pernicious Anaemia and Pituitary Insufficiency, Lancet **2**:307, 1942.

56. Skavlem, J. H., and Storey, C. H.: Concurrent Tuberculosis and Pernicious Anemia, Ohio State M. J. **38**:142, 1942.

sequent roentgen examinations, the absence of tubercle bacilli in the sputum and the stomach washings and the subsequent favorable course.

In a study of 20 patients with pernicious anemia whose hematocrit readings on erythrocytes varied from 11 to 35 per cent, Warner and Owen [57] found the prothrombin level to be between 40 and 65 per cent of normal in a majority of the patients, according to the two stage method of Warner, Brinkhous and Smith. When vitamin K was administered in the form of synkamin (4-amino-2-methyl-1-naphthol hydrochloride) either orally or intravenously, no significant change followed. There was a loose correlation between the severity of the anemia and the degree of the hypoprothrombinemia, as there was some tendency for the lowest values to occur in the cases in which the anemia was most severe. No correlation was demonstrable between the degree of hypoprothrombinemia and the amount of damage of the nervous system. The lowest prothrombin level observed in these cases was 40 per cent of normal, which is above the level at which bleeding ordinarily occurs, and there was no evidence of a hemorrhagic tendency. The author states that the clotting power of the blood as measured by the one stage method of Quick or the "bedside" method of Ziffren, Owen, Hoffman and Smith was found to be within normal limits and was not modified by therapy. The interpretation of the failure of the one stage and two stage methods to agree in certain conditions is not known. The beneficial effect of liver extract is possibly attributable to an improvement of the function of the liver. Some evidence is at hand which suggests a mild hepatic insufficiency in cases of pernicious anemia. It is of interest to note that the beneficial effect of liver extract on the production of prothrombin is limited to cases of pernicious anemia; the hypoprothrombinemia observed in newborn infants, in patients with Laennec's cirrhosis, in those with obstructive jaundice and in debilitated patients does not respond to this form of therapy.

An interesting series of comparisons has been made by Strauss and Burchenal [58] of the red blood cell counts and hemoglobin determinations on the capillary and the venous blood of patients with pernicious anemia whose disease was in therapeutically induced remission. The results of a total of 2,139 blood examinations when analyzed revealed that the mean capillary red blood cell count of 80 patients was 4,690,000 per cubic millimeter and the mean venous red blood cell count 4,444,000 per cubic millimeter, a difference of 246,000 per cubic millimeter. This value they consider to be statistically significant, as there is less than 1 chance in 1,000 of its being accidental. The mean of the hemoglobin determinations on the capillary blood of the 80 patients was 91.8 per cent (15.6 Gm. per hundred cubic centimeters equals 100 per cent), whereas the mean of the hemoglobin determinations on the venous blood of these patients was 87.3 per cent. They consider that the difference of 4.5 per cent is likewise significant, as here also there is less than 1 chance in 1,000 that it is accidental. They conclude, therefore, that the venous blood of patients with pernicious anemia under treatment has approximately 5 per cent less erythrocytes and hemoglobin than the blood obtained from the capillaries. According to the observations reported by Wintrobe and Miller in 1929, the hemoglobin value and the red blood cell count for adult man are the same whether the blood is obtained from the ear or the finger or a vein without stasis. Strauss and Burchenal apparently are not convinced that this is

57. Warner, E. D., and Owen, C. A.: Hypoprothrombinemia in Pernicious Anemia, Am. J. M. Sc. **203**:187, 1942.

58. Strauss, M. B., and Burchenal, J. H.: Comparison of Capillary and Venous Red Blood Cell Counts and Hemoglobin Determinations in Patients with Pernicious Anemia in Remission Under Treatment, J. Lab. & Clin. Med. **27**:937, 1942.

true, for they state that the difference they observed in patients with pernicious anemia may also hold for normal persons, but their data are insufficient to prove this point.

In a previous study Ørskov found that the red blood cells of patients with pernicious anemia showed altered permeability to dextrose, which was corrected by liver therapy. There were two possible explanations: Either the anti-pernicious-anemia factor acted directly on the red blood cells, or new red blood cells with normal permeability were formed. To find out which of these explanations was correct, Ørskov [59] carried out experiments in which liver and desiccated hog stomach were fed by mouth to healthy subjects and the permeability of the red blood cells determined. It was found that the permeability was affected in the same manner as in patients with pernicious anemia, and since the maximum effect was attained on the day following feeding, it was concluded that the anti-pernicious-anemia factor acts directly on the permeability of the red blood cells.

Cooke [60] reports the rather unusual case of a woman aged 30 years with pernicious anemia in which the diagnosis was questioned when she was first observed, because there was apparently a spontaneous reticulocyte rise of 30 per cent. This, with the acute onset and the fact that the patient had experienced previous attacks with jaundice, suggested the diagnosis of hemolytic jaundice. Subsequently all findings indicated beyond the question of a doubt that the patient did have true addisonian pernicious anemia. This case brings up the interesting point of the extent of the reticulocyte rise in such patients when their disease is in spontaneous remission. Unfortunately, it is not usual to observe patients at this time. The author offers the suggestion that relapses and remissions may be correlated with varying amounts of the intrinsic factor, which in turn may be associated with variations in the intensity of the gastritis. This, of course, raises the fundamental question as to just what is the cause of the diminution of intrinsic factor in the disease or, in other words, what is the real underlying cause of the disorder. The possibility that gastritis may influence the amount of the intrinsic factor cannot be denied. We should like to emphasize also that variations in the amount of the anti-pernicious-anemia factor might be associated with quantitative changes in the extrinsic factor in the diet.

Arneth [61] has written an article which is mainly a plea for the utilization of the simple laboratory means of examining the blood in the diagnosis of pernicious anemia. He finds the changes thus observed reliable, within the reach of every physician, and present even before the characteristic alterations occur in the marrow. Special emphasis is laid on the "shift to the right" in the Arneth count and on the diminution in the total number of polymorphonuclear cells. As pronounced leukopenia is a feature of the disease during relapse, there is diminution in other types of white blood cells, as well as in neutrophils.

Macrocytic Anemias Related to Pernicious Anemia.—A complete summary of present knowledge of the macrocytic anemias is presented by Watson,[62] in which a discussion of their etiology, classification and treatment is given. In his opinion, such anemias should be separated into two main groups, namely, those with

59. Ørskov, S. L.: Untersuchungen über die Wirkung von per os zugeführtem Leberextrakt und Ventrikelschleimhaut auf die Permeabilität der roten Blutkörperchen beim normalen Menschen, Acta physiol. Scandinav. **3**:82, 1941.

60. Cooke, W. T.: Unusual Reticulocytosis in Untreated Case (Diagnostic Difficulty), Brit. M. J. **2**:806, 1941.

61. Arneth, J.: Ueber die qualitativen Blutbefunde bei der perniziösen anämischen Reaktion (perniziösen Anämie) München. med. Wchnschr. **89**:371, 1942.

62. Watson, C. J.: Macrocytic Anemia, Illinois M. J. **82**:195, 1942.

megaloblastic and those with normoblastic marrow. He believes that diffuse megaloblastic hyperplasia is indicative of deficiency or of poor utilization of the erythrocyte-maturing factor and that it is an indication for use of liver extract. According to the author, the present day concept of addisonian anemia includes: atrophic gastritis and achylia, which is often associated with glossitis; a constitutional (familial) factor; the resultant lack of intrinsic factor; a continued need of and response to liver therapy. It is considered that the appearance of the anemia may be hastened or precipitated by such factors as deficient intake of animal protein, loss of teeth or change in economic status. This implies that the intrinsic-extrinsic factor relationship obeys the laws of mass action, which in the author's opinion is correct. "Achrestic" anemia due to defective utilization of the erythrocyte-maturing factor, as described by Wilkinson, is apparently accepted by Watson with reluctance, as he says he hopes to "deemphasize" it. We agree that it must be an exceedingly rare syndrome in this country. The macrocytic anemias with normoblastic marrow include those of the hemolytic type, both primary and secondary, and those without increased hemolysis. He emphasizes that from the standpoint of therapy the macrocytic anemias should be considered as normochromic or hypochromic. Iron therapy is indicated in the latter, and liver extract, in both groups if the marrow is megaloblastic.

Ten patients with severe degrees of macrocytic anemia and with free acid present in the gastric secretions were studied at the nutrition clinic of the Hillman Hospital by Moore and his associates.[63] All but 1 of the patients showed or had shown the clinical manifestations of pellagra. In 2 patients there was the clinical picture of nontropical sprue, 1 patient had a beef tapeworm, and 5 patients were relieved of their diarrhea when nicotinic acid was given. In each patient there was a pronounced shift in the marrow to the younger red cell elements, with a striking increase in megaloblasts. In all instances there was a decided dietary deficiency of animal proteins. It was demonstrated that the intrinsic factor was present in the gastric secretions of 3 patients. Six responded submaximally to the administration of 250 Gm. of raw beef muscle. After one week of a diet known to be deficient in animal protein and in vitamin B complex, the crystalline members of this complex were given orally and parenterally without effect on the red blood cells, the marrow or the reticulocytes. An 80 per cent alcoholic extract of beef muscle which was "practically protein free" but known to contain the extrinsic factor produced a rise in reticulocytes and a slight increase in red blood cells. A secondary rise was then obtained in several of the cases by daily administration of the same amount of beef muscle extract which had been incubated with 100 cc. of normal human gastric juice. After completion of the observations just described, daily parenteral administration of 4 to 6 units of liver extract produced in 9 of the 10 patients a significant increase in the reticulocytes and an acceleration of the formation of red blood cells. These important observations were interpreted as indicating (1) that macrocytic hyperchromic anemia without achlorhydria occurs not infrequently in the southern states where pellagra is endemic and (2) that the anemia is produced both by a dietary deficiency of the extrinsic factor and by poor absorption from the intestinal tract.

Heath[64] considers a group of macrocytic anemias which resemble pernicious anemia but stand apart from this disease because they do not respond favorably to liver extract. He includes in this group macrocytic anemia due to carcinoma,

63. Moore, R. A.; Spies, T. D., and Cooper, Z. K.: Pellagra: Histopathology of Skin in Pellagra, Arch. Dermat. & Syph. **46**:100 (July) 1942.

64. Heath, C. W.: Refractory Anemias, Bull. New England M. Center **4**:11, 1942.

osteosclerosis, the "achrestic" anemia of Wilkinson, the macrocytic anemia sometimes associated with cirrhosis of the liver, and agnogenic myeloid metaplasia of the spleen as recently described by Jackson, Parke and Lemon. He also lists the following conditions which may be accompanied by macrocytosis: acute loss of blood, various hemolytic anemias, hemoglobinuria, various anoxemias, acute heart failure occurring terminally, anemia of infection, anemia of nephritis, myelophthisic anemias and various forms of poisoning. An attempt has been made by the author to distinguish between treatable and refractory macrocytic anemias by a study of the diameters of the erythrocytes. This differential point was suggested by the observation that anisocytosis is usually greater in true pernicious anemia than in certain refractory macrocytic anemias. In this study only cases of macrocytic anemia in which the mean corpuscular volume was 100 cubic microns or greater were utilized. By measuring the diameters of the red blood cells according to the technic of Price-Jones, it was found that below the level of 2,000,000 red blood cells per cubic millimeter the standard deviation of the diameters is helpful in distinguishing pernicious anemia from other macrocytic anemias. The critical level of standard deviation is about 0.9 cubic micron. The deviation is above this level in most cases of pernicious anemia and below it in most cases of severe refractory macrocytic anemia. A second point is helpful in studying the Price-Jones curves. On inspection these curves are not symmetric but are skewed to the right or to the left. It was found that in most cases of pernicious anemia the curve was skewed to the left, whereas in cases of refractory macrocytic anemia the curve is either not skewed or is skewed to the right.

Limarzi [65] reviews the recent advances in the diagnosis and treatment of abnormal conditions of the blood and classifies all cases of anemia into four groups as follows: (1) macrocytic anemia in which the mean corpuscular volume is greater than 94 cubic microns and the mean corpuscular hemoglobin concentration is approximately 30 per cent; (2) normocytic anemia in which the mean corpuscular volume is between 80 and 94 cubic microns and the mean corpuscular hemoglobin concentration is 30 per cent or greater; (3) simple microcytic anemia in which the mean corpuscular volume is less than 80 cubic microns and the mean corpuscular hemoglobin concentration is 30 per cent or higher; (4) hypochromic microcytic anemia in which the mean corpuscular hemoglobin concentration is 29 per cent or less and the mean corpuscular volume is greatly or little reduced or even actually normal. The following diseases are included in the four groups: pernicious anemia, cirrhosis of the liver, sprue, pregnancy, fish tapeworm disease, aplastic anemia, acute leukemias, pellagra, hypothyroidism, carcinoma of the stomach, metastatic lesions of the marrow, lymphoblastomas, agranulocytosis, nephritis, celiac disease, sickle cell anemia, Cooley's anemia and erythroblastosis. Doubtless the author means to indicate that some of these conditions are always associated with macrocytic anemia whereas others may cause macrocytic anemia at times. The article gives a résumé of current knowledge concerning the various types of macrocytic anemia with special reference to pernicious anemia.

Berghausen [66] emphasizes that macrocytic anemia may result from a number of causes and that a careful diagnostic study should be made before intensive therapy is initiated. He reports and discusses 5 cases of severe anemia.

65. Limarzi, L. R.: Recent Advances in the Diagnosis and Treatment of Abnormal Blood Conditions, Illinois M. J. **81**:296, 1942.

66. Berghausen, O.: Macrocytic Anemia: Case Reports, Cincinnati J. Med. **22**:547, 1942.

Gordon and Japa [67] report 2 cases of unusual interest in which severe macrocytic anemia developed following gastroenterostomy. One patient, aged 52, had been operated on eleven years before, for a duodenal ulcer. The red blood cell count was 1,630,000 per cubic millimeter and the hemoglobin value was 40 per cent. The sternal puncture revealed normal marrow. Liver therapy produced a good result. A second patient, aged 62, had undergone gastroenterostomy twenty-five years before the development of severe macrocytic anemia. He was benefited with liver extract. The red blood cell count was 1,500,000 per cubic millimeter; the hemoglobin value was 55 per cent; aspirated sternal marrow showed an excessive number of erythroblasts. Achlorhydria was present. The authors believe that it is preferable to speak of these patients as showing macrocytic anemia rather than true pernicious anemia. They state that the condition may have arisen from two causes: first, a lack of intrinsic factor; second, an interference with the flow of intestinal contents, which might interfere with the interaction of the intrinsic and extrinsic factors and impair absorption of the erythocyte-maturing substance. In criticism of this article Brown [68] makes the following pertinent statements: (1) that the first patient may have had macrocytic anemia but that no facts are given to support this, and that the color index is not helpful unless there is an accompanying statement with reference to the hemoglobin standard used; (2) that the response to liver therapy in a case of anemia in which the sternal marrow is "normal" is sufficiently unusual to justify the inclusion of the hematocrit reading of the packed cell volume, from which the volume of the cells could be calculated; (3) that a note on the criteria of the "good results" which followed the liver therapy would also have been of interest. We are in sympathy with the criticisms expressed by Brown in all instances in which insufficient data are presented by which the reader may evaluate the situation for himself rather than accept statements which merely interpret the findings without presenting them in detail.

Samuel [69] reports the case of a patient who had suffered from chronic gastric ulcer for several years and in December 1936 was treated by cholecystectomy. In June 1938 the man was found to have pernicious anemia. He reacted well to liver therapy. In November he had a severe attack of ulcer pain, which was soon followed by recrudescence of the chronic ulcer distress. The author makes the suggestion that possibly "the production of the intrinsic factor may be interfered with by gastric (and, possibly by hepatic) lesions." Detailed blood findings, the results of gastric analysis and other data which might enable one to make a critical evaluation of the author's statements are not presented. Never in our experience has there been an instance of pernicious anemia and peptic ulcer occurring in the same patient. In one condition there is always achlorhydria, perhaps present from birth, and in the other there has invariably been free hydrochloric acid in the gastric secretions. It is entirely possible that the patient may have had macrocytic anemia associated with hepatic disease or with some anomaly of the intestinal tract, but it is unlikely that true addisonian pernicious anemia and peptic ulcer were both present.

The case of a 64 year old man on whom gastroenterostomy was performed after accidental "swallowing of spirits of salts" is reported by Harlem.[70] Four-

67. Gordon, N. S., and Japa, J.: Macrocytic Anaemia Following Gastro-Enterostomy, Brit. M. J. **2**:769, 1941.

68. Brown, A.: Macrocytic Anaemia Following Gastro-Enterostomy, Brit. M. J. **1**:127, 1942.

69. Samuel, B.: Macrocytic Anaemia After Gastro-Enterostomy, Brit. M. J. **1**:55, 1942.

70. Harlem, I. C.: Macrocytic Anaemia After Gastro-Enterostomy, Brit. M. J. **1**:739, 1942.

teen years later evidence of pernicious anemia developed with a hemoglobin value of 60 per cent. The number of red blood cells per cubic millimeter was not determined, but measurements demonstrated that the anemia was macrocytic in type, for the average diameter of the cells was 8.5 microns. There was a satisfactory clinical response to intramuscular injections of liver extract. The title, "Macrocytic Anaemia After Gastro-Enterostomy," implies a causal relation between the surgical operation and the anemia, although a period of fifteen years intervened. This assumption appears unwarranted, first, because of the long interval and, second, because of the scarcity of examples of such a relation in the large number of cases in which gastroenterostomy has been performed in the past few decades.

It is stated by Wayburn [71] that there is a lack of agreement in the literature concerning the incidence of macrocytosis in hepatic disease. In regard to Laennec's cirrhosis alone, for example, the more recent figures vary from 41 to 90 per cent. This difference of opinion is attributed in part to the difference in criteria and in classification of the condition involved, and in part to the difference in methods employed in determining macrocytosis. According to the author, the use of determinations of volume is superior, as the lesser degrees of enlargement of cells are detected most readily by volumetric measurements. Ten of 11 patients with acute hepatitis and 12 of 16 with Laennec's cirrhosis had macrocytosis. Of the total of 27 patients, 82 per cent showed macrocytosis. Anemia, if present, was slight, the lowest hemoglobin content being 74 per cent (12.5 Gm.). The macrocytosis frequently persisted despite treatment, return of the blood count to normal and disappearance of all symptoms. According to the author, the explanation of the macrocytic anemia on the basis of simple failure to store hemopoietic substance in the diseased liver seems inadequate. He suggests that the phenomenon results partly from deficiency of the extrinsic factor and partly from inability of the liver to synthesize the maturation factor.

The case of an Australian soldier in whom macrocytic anemia developed in association with splenomegaly and a prolonged febrile illness due to infective hepatitis is reported by Bonnin.[72] This patient was one of a number who suffered from the disease but was the only one noted to have macrocytic anemia. About five weeks after the onset the hemoglobin value was 70 per cent (Sahli), the red blood cell count 2,200,000 per cubic millimeter and the color index 1.6. The intramuscular injection of various types of liver extract was followed by a typical reticulocyte response and a return of the blood to normal. Eventually the patient made a complete recovery. The anemia was considered to be due to deficiency of the anti-pernicious-anemia factor associated with extensive damage of the liver, possibly complicated with excessive destruction of blood.

A comprehensive survey is made by Harris and Harris [73] of the genesis of pellagra, pernicious anemia and sprue. It is their belief that these three conditions are not different manifestations of the same disease but three separate entities. It is conceded, however, that the three appear to be allied nutritional disorders. It is also stated that if the dermatologic manifestations of pellagra are absent, this disease, sprue and pernicious anemia as manifested in oral and gastrointestinal symptoms are indistinguishable from one another. The authors maintain that pathologic change of the liver, usually fatty degeneration, is an almost

71. Wayburn, E.: Macrocytic Anemia in Liver Disease, California & West. Med. **56**:130, 1942.

72. Bonnin, J. M.: Macrocytic Anaemia Occurring in Case of Infective Hepatitis, M. J. Australia **1**:637, 1942.

73. Harris, S., and Harris, S., Jr.: The Genesis of Pellagra, Pernicious Anemia and Sprue, Am. J. Digest. Dis. **9**:29, 1942.

constant finding in pellagra, in pernicious anemia and, to a less extent, in sprue. Atrophy of the stomach and intestines may be found in all three diseases. When changes are present in the spinal cord in any of these diseases, the lateral and posterior columns are involved. A review is given of reported cases in which two or all three of these disorders occurred in the same patient. According to them, this coincidence suggests common etiologic factors.

Hawes,[74] in an article on sprue and allied disorders, regards several conditions of unknown cause affecting fat metabolism as one entity. In this group he includes celiac disease, idiopathic steatorrhea, nontropical sprue and tropical sprue. According to him, in most cases of steatorrhea anemia is prominent and may assume an erythroblastic, aplastic, hypochromic or a macrocytic, hyperchromic picture. In some cases steatorrhea is indistinguishable from pernicious anemia, and in others the blood picture may change from hypochromic to hyperchromic or from macrocytic hyperchromic to hypochromic. The cause of these changes is unknown, but the tendency is for the hypochromic variety to become macrocytic and hyperchromic as the disease advances, especially if the diarrhea persists. Under treatment with liver or liver extract, hyperchromic macrocytic anemia often changes to hypochromic anemia, and if then large doses of iron are given, the blood picture returns to normal.

Anemia occurs in virtually all cases of untreated sprue, according to Shookhoff.[75] The macrocytic anemia of the disease may be divided into three types, as follows: (1) that responding to orally administered extrinsic factor; (2) that not responding on the oral administration of this factor but yielding to orally administered liver extract; (3) that responding only on parenteral therapy. It is inferred, therefore, that the macrocytic anemia of sprue may be due to deficiency of the extrinsic factor, reduction in the intrinsic factor, failure of adequate absorption of the hemopoietic principle or a combination of two or all of these mechanisms. Furthermore, some patients with sprue have hypochromic anemia, but the author does not know whether this is to be attributed to inadequacy of the intake of iron or to impairment of the absorption of this element.

Abrahams [76] reports the case of a young woman, 19 years old, with idiopathic steatorrhea, severe macrocytic anemia and glossitis. The red blood cell count was 2,140,000 per cubic millimeter, and the hemoglobin content, 20 per cent. The color index was 1.2, and the average diameter of the red cells was 7.9 microns. Recovery followed the administration of a low fat diet, autolyzed yeast (marmite), pills of ferrous carbonate (Blaud's pills), calcium lactate, vitamins A and D, and transfusions of blood.

Assay of Antianemic Materials on Animals.—The study of Stasney and Burns [77] is another attempt to obtain a method of bioassay for the anti-pernicious-anemia factor, other than the utilization of untreated patients with the disease. They have employed the marsupial opossum because, after an intrauterine life of about twelve days, the immature offspring live in the maternal pouch for an additional ninety days and hence are accessible for the direct injection of anti-pernicious-anemia substance. The fundamental basis for the study is that the

74. Hawes, R. B.: Sprue and Allied Disorders, Practitioner **149**:157, 1942.

75. Shookhoff, H. B.: The Blood Picture in Sprue, Rev. Gastroenterol. **9**:338, 1942.

76. Abrahams, A.: Idiopathic Steatorrhea with Severe Anemia and Pyrexia, Proc. Roy. Soc. Med. **35**:11, 1941.

77. Stasney, J., and Burns, E. L.: Influence of Active and Inactive Antianemic Principles upon Erythrocytes of Immature Opossum (Didelphys Virginiana), Am. J. M. Sc. **203**:191, 1942.

erythrocytes of patients with pernicious anemia and those of mammalian fetuses are similar in some respects, so that the activity of the anti-pernicious-anemia substance might be measured by an acceleration of the rate of maturation of the fetal erythrocytes. Extensive observations showed that the immature developing opossum, living in the maternal pouch, did have macrocytic anemia, which disappeared in adult life. The direct injection of either concentrated normal human gastric juice or liver extract reduced the mean "maximal" diameter, and the mean corpuscular volume significantly and increased the number of erythrocytes. On the other hand, these changes did not follow the injection of inactivated normal human gastric juice or liver extract or the gastric juice from a patient with addisonian pernicious anemia. These results seem promising, but reference should be made to the study of Last and Hays,[78] in which confirmatory results were not obtained. The latter emphasize, as others have done, the great desirability of a readily available method of assay for the anti-pernicious-anemia factor and turn to a study of the effect of the principle on the maturation of embryonic blood cells as a possible help in this direction. They emphasize that the primitive generation of erythrocytes in the embryo, though morphologically similar to the megaloblastic generation of pernicious anemia, is not identical with it. The possibility, however, that embryonic megaloblastic and erythroblastic erythropoiesis might respond similarly to liver therapy has stimulated interest in the fetal approach to the bioassay problem. Their own studies have been an attempt to confirm the positive findings in the young of the opossum pouch and 11 day rat fetuses. Contrary to other reports, however, no accelerated maturation of the erythrocytes as reflected by a significant decrease of the mean corpuscular volume was observed in the pouch young receiving liver therapy, nor were positive results obtained when 15 and 20 day rat fetuses were employed. They conclude that the embryogenesis of blood in the opossum and the rat is unaffected by the anti-pernicious-anemia principle and that neither embryo should be utilized in the bioassay of anti-pernicious-anemia preparations. In discussing the negative results obtained in the fetal approach to the bioassay problem the authors point out a fallacy in its rationale, namely, that the immature cell of the premature embryonic and that of the megaloblastic generation are not cytologically identical and that, furthermore, the macrocytes in the blood of patients with pernicious anemia reflect a megaloblastic erythropoiesis which is an abnormal phenomenon, whereas the large erythrocytes in embryonic blood are the mature elements of a primitive system of erythropoiesis which is a normal physiologic process. We consider that, alluring as the fetal method of bioassay may seem when first considered, the objections cited appear to be valid.

An article by Hays, Last and Koch[79] summarizes their observations of the effect of liver extract on erythropoiesis in the chick embryo. It is advantageous to use the chick embryo as the liver fraction can be injected directly into it without depending on placental transfer and, in addition, the absolute age is known with certainty. They conclude, however, after careful studies, that the rate of erythropoiesis in the 3 to 7 day old chick embryo cannot be utilized as a specific means of assay for liver extract, as the changes observed are not statistically significant.

78. Last, J. H., and Hays, E. E.: The Action of the Antipernicious Anemia Principle on the Blood Picture of Opossum Pouch-Young and Rat Embryos, Am. J. M. Sc. **203**: 836, 1942.

79. Hays, E. E.; Last, J. H., and Koch, F. C.: Effect of Liver Extracts upon Erythropoiesis in Chick Embryo, Am. J. M. Sc. **203**:843, 1942.

Pace and Fisher [80] attempted to correlate the U. S. P. unitage of liver extract with the method of assay for this material devised by Overbeek, Gaillard, deJongh and Yam. This method depends on measurement of the migration of cells from isolated living guinea pig marrow, embedded in a coagulum of plasma, to which various concentrations of liver extract have been added. At certain optimal concentrations of liver extract the migration is increased, and the concentration thus effective is taken as an index of the potency of the liver extract. From the results obtained, a curve was constructed which shows the relation between the dilutions of liver concentrates at which maximal migration of cells from the marrow occurred and the U. S. P. potency of these concentrates. They are of the opinion that this curve may be utilized for the determination of the expected clinical potency of an unknown liver extract.

HYPOCHROMIC ANEMIA

Incidence in Adults and Children.—Restrictions of diet imposed by the exigencies of wartime have raised the question, particularly in England, of the incidence of anemia attributable to iron deficiency. A survey of the hemoglobin values of 1,074 women and children, residents of London and English rural areas, was conducted by Mackay, Dobbs, Wills and Bingham.[81] The age range of the children was 6 months to 18 years. The women included housewives, hospital nurses, medical students and factory workers. The findings of Mackay and her associates when compared with the results of surveys made prior to the war indicated a decrease in hemoglobin presumably attributable to wartime diets, deficient in protein and iron. The differences were not great but appeared to be significant. The incidence of hypochromic anemia was greater among women and children living in the country than in residents of London. In a similar study Davidson and others [82] determined the hemoglobin levels of 831 infants, preschool children and school children of working class families living in Edinburgh, Scotland. The same type of investigation had been carried out in Edinburgh before the war. The authors found that after three years of wartime restrictions no change in hemoglobin levels had occurred in infants but that a decline was observable in older children. They conclude that during peacetime the chief factor influencing nutrition is the economic status of the family, but that in wartime food rationing and the difficulties of obtaining unrationed foods are the most important factors, irrespective of income.

The hemoglobin values of school children in Southern Rhodesia, South Africa, were determined by Jones.[83] The Newcomer method was employed, and a range of 12.0 to 14.9 Gm. of hemoglobin per hundred cubic centimeters of blood was adopted as normal. On this basis, the incidence of anemia among 2,173 European children was 14.7 per cent, and that among 304 Negro children was 23 per cent. The predominant factors causing anemia were considered to be faulty diet and parasitic infection. Morales [84] examined the blood of 104 Puerto Rican girls

80. Pace, N., and Fisher, R. S.: Assay of Anti-Pernicious Anemia Liver Concentrates by the Use of an Isolated Bone Marrow Preparation, J. Pharmacol. & Exper. Therap. **74**: 256, 1942.

81. Mackay, H. M. M.; Dobbs, R. H.; Wills, L., and Bingham, K.: Anaemia in Women and Children on War-Time Diets, Lancet **2**:32, 1942.

82. Davidson, L. S. P., and others: Nutritional Iron Deficiency Anaemia in Wartime: The Haemoglobin Levels of Eight Hundred and Thirty-One Infants and Children, Brit. M. J. **2**:505, 1942.

83. Jones, E. B.: Sub-Clinical Anaemia of School-Children in Southern Rhodesia, Tr. Roy. Soc. Trop. Med. & Hyg. **36**:99, 1942.

84. Morales, F. H.: Blood Studies in Puerto Rican Children, Puerto Rico J. Pub. Health & Trop. Med. **17**:387, 1942.

between the ages of 8 and 18 years. He found subnormal blood values for 82 per cent of these girls. The anemia was macrocytic in 52 per cent and hypochromic in 38 per cent. The diets of these subjects were low in calories, protein and minerals, including iron. No attempt was made to estimate the intake of vitamins.

No relation between the hemoglobin level and the daily intake of vitamin C was found by Thomson, Glazebrook and Millar [85] in a study of adolescent boys living in an institution. The diet of all the subjects was low in vitamin C, but one group was given the vitamin as a medicinal supplement. Apparently, determinations of blood ascorbic acid were not performed.

A case of idiopathic hypochromic anemia occurring in a man is reported by Currie.[86] The patient was 28 years old, his diet was considered to have been average in quality and quantity and he had no evidence of hemorrhage. Achlorhydria was found; the erythrocyte count was 3,700,000 per cubic millimeter, and the hemoglobin, 48 per cent. The sternal marrow was normoblastic. A reticulocyte response with increase in blood values followed treatment with iron and ammonium citrates. In a young male this type of blood picture not associated with demonstrable loss of blood is most unusual and always raises the question of occult hemorrhage. We have observed such patients who proved to have intermittent bleeding from intestinal telangiectases. The case of a man 46 years old with severe hypochromic anemia, achlorhydria and koilonychia is reported by Clarke.[87] The patient had bleeding hemorrhoids, his symptoms were attributable entirely to the anemia, his heart was enlarged, his tongue was beefy red and he showed no evidence of neurologic change. Recovery followed administration of iron and ammonium citrates, 4 Gm. daily, but the anemia recurred when treatment was taken irregularly. Following a second remission, induced by ferrous sulfate, 1 Gm. daily, the return of hydrochloric acid in the gastric secretions was observed.

The regeneration of hemoglobin after donations of blood was studied by Fowler and Barer.[88] After an average withdrawal of 555 cc. the mean decline of hemoglobin in 200 donors was 2.3 Gm. per hundred cubic centimeters. In the majority of instances the predonation level was restored in less than fifty days, but 25.8 per cent of the subjects required more than two months for complete recovery. The rate of regeneration was not retarded after multiple donations. It was slower in females than in males. The administration of iron and ammonium citrates, 1 Gm. daily, was accompanied by an increase in the average daily regeneration of hemoglobin amounting to 49 per cent, and the period of recovery was shortened from an average of forty-nine and six-tenths to one of thirty-five and two-tenths days after the initial withdrawal of blood. Following subsequent donations, treatment with iron had progressively less effect on the period of recovery.

In an extraordinary article Gottlieb [89] reports on evaluation of therapy in cases of hypochromic anemia. He draws the conclusion that iron salts alone are of

85. Thomson, S.; Glazebrook, A. J., and Millar, W. G.: Vitamin C and Anaemia, with Description of Photoelectric Colorimeter, J. Hyg. **42**:103, 1942.

86. Currie, J. P.: Idiopathic Hypochromic Anaemia in a Male Adult, Brit. M. J. **1**: 762, 1942.

87. Clarke, B. G.: Hypochromic Anemia with Koilonychia (Spoon Nails): Report of Case, New England J. Med. **227**:338, 1942.

88. Fowler, W. M., and Barer, A. P.: Rate of Hemoglobin Regeneration in Blood Donors, J. A. M. A. **118**:421 (Feb. 7) 1942.

89. Gottlieb, R.: Whole Liver as an Adjuvant to Iron in the Treatment of Hypochromic Anaemia, Canad. M. A. J. **47**:456, 1942.

value only in the treatment of patients who have been anemic for a short time. Presumably this group includes those with acute loss of blood. In patients whose hypochromic anemia is more chronic, medicinal iron supplemented by the vitamin B complex is of temporary value, regardless of the quality of the diet, but the anemia tends to recur on discontinuance of the medication. He reports that a proprietary preparation containing iron and a liver concentrate, which is misleadingly termed "whole liver," provides a beneficial effect which persists after the discontinuance of treatment and "is apparently capable of compensating for shortcomings in the diet." This contribution, so contrary to the recorded experience of clinicians generally, would scarcely warrant mention were it not for the widespread publicity which is accorded to such reports through commercial channels. Physicians generally should realize that the only medicinal agent of clinically proved value in the treatment of hypochromic anemia is iron but that in cases in which dietary deficiencies occur therapeutic management should be based on appraisal of the individual nutritional status. Castle [89] states, "Iron, therefore, appears to be the only agent of practical importance in the treatment of hypochromic anemia." Hoffman and Kracke [90] state, "Mixed shotgun therapy is entirely unwarranted and it is extremely expensive for the patient." Other recent articles dealing with the treatment of hypochromic anemia and confirming the therapeutic value of unsupplemented iron salts have been published by Fowler,[91] Bethea [92] and Beard.[93]

Anemia in Pregnancy.—According to Peralta-Ramos and Gascon,[94] Hippocrates observed the pallor of pregnant women and attributed it to the additional drain of the fetus. H. Nase, in 1836, was the first to find evidence of a decrease in the number of erythrocytes during pregnancy, and he attributed it to an increase in plasma volume. Numerous studies by many investigators have upheld the essential truth of these observations. The present authors examined the blood of 1,012 women in Argentina at intervals throughout gestation and arrived at the following conclusions: The majority of healthy pregnant women show a decrease in the concentration of circulating erythrocytes beginning during the first month and reaching a maximum at the ninth month of gestation; the hemoglobin level is also lowered, but the rate of decline becomes slowed during the last trimester. Determinations of the freezing point of the plasma, the concentration of the plasma proteins, the concentration of bilirubin and the number of circulating monocytes lent support to the view of the authors that the oligocythemia occurring during pregnancy is due to a physiologic increase in the destruction of red blood cells rather than to hemodilution. We agree that the evidence indicates increased breakdown of erythrocytes during pregnancy but believe that ordinarily this change is compensated for by more active regeneration of erythrocytes. On the other hand, increased volume of plasma has been demonstrated by numerous quantitative studies and can readily explain the physiologic oligocythemia of pregnancy.

The hemoglobin levels of 392 pregnant women were determined by Hamilton and Wright [95] at intervals from about the third month to the termination of

90. Hoffman, B. J., and Kracke, R. R.: The Diagnosis and Treatment of Hypochromic Anemias, South. Med. & Surg. **104**:1, 1942.

91. Fowler, W. M.: Iron Deficiency Anemias, Clin. Med. **49**:74, 1942.

92. Bethea, J. M.: Uses and Misuses of Iron and Liver Extracts in Treatment of Anemias, Memphis M. J. **16**:187, 1941.

93. Beard, M. F.: Treatment of Anemia, Kentucky M. J. **40**:161, 1942.

94. Peralta-Ramos, A., and Gascon, A.: A proposito de la seudo-anemia del embarazo, Prensa méd. argent. **29**:929, 1942.

95. Hamilton, H. A., and Wright, H. P.: Development of Hypochromic Anaemia During Pregnancy: Response to Iron Therapy, Lancet **2**:184, 1942.

gestation. Iron and ammonium citrates, 6 Gm. daily, were administered to one half of the group except for certain ones who received ferrous sulfate. The average hemoglobin level of the untreated subjects showed a decline, whereas that of the treated women was elevated. A comparison with data acquired earlier on a similar class of subjects led the authors to the conclusion that the incidence of anemia among pregnant women of the artisan class was higher than before the war. The change was attributed to nutritional deficiency, and routine prenatal administration of iron as a prophylactic measure, as well as improvement of the diet, was advocated. A similar conclusion was reached by Thomas [96] as a result of determinations of hemoglobin in cases of pregnancy.

In Coorg, India, considered an unhealthy locality, low hemoglobin values among pregnant women and children are exceedingly prevalent, according to Bhave and Bopaiya.[97] The deficiency is attributed to poor diet and to malarial and hookworm infection, and was remedied by administration of medicinal iron. A monograph of 135 pages on the incidence, the type and the response to therapy of anemia observed in 529 pregnant women in Calcutta, India, has been published by Napier and Neal-Edwards.[98] The data are considered with reference to age, parity, nutritional status, religion and other attributes of the subjects and are too involved and extensive to be reviewed here. This most complete study should, however, serve as a valuable reference.

Sixteen cases of macrocytic anemia occurring in pregnant women are reported and described by Davidson, Davis and Innes.[99] Macrocytosis, anisocytosis and presence of oval erythrocytes were not as prominent in the blood of these patients as in that of patients with true pernicious anemia. Sternal aspiration revealed a megaloblastic reaction of the marrow in all but 1 of the 13 cases in which it was performed. A temporary refractory period followed institution of parenteral liver therapy in 10 of the patients, but eventually all responded. The authors suggest that the transient arrest of erythropoiesis may have been due to the absence of some factor not supplied by liver extract and possibly contained in protein or that the delay in therapeutic response may have been due to inability of the marrow to utilize the hematinic principle of liver as a result of the strain of pregnancy and the shock of labor in a severely anemic woman. A decided drop in the blood values of these subjects was observed after delivery.

One hundred and three cases of macrocytic anemia occurring in pregnant women in India are reported by Mudaliar and Menon.[100] The subjects were of varied economic status and dietary habits. No deficiency of protein or of vitamin B complex was recognized, but the diets generally appeared to be inadequate in vitamins A, C and D. Anemia of macrocytic type was observed more frequently in multiparas than in primiparas and was recognized usually in the second or the third trimester. The color index was more often above than below unity. Contrary to the reported experience of others, the authors found autolyzed yeast (marmite) of no therapeutic value. Crude and refined concentrated liver extracts were equally effective in relieving the anemia, but in some instances there was no response

96. Thomas, R. C.: Haemoglobin of Pregnant Women, Brit. M. J. **1**:88, 1942.

97. Bhave, P. D., and Bopaiya, M. S.: Diet Surveys and Investigations of Haemoglobin Levels in Coorg, Indian J. M. Research **30**:53, 1942.

98. Napier, L. E., and Neal-Edwards, M. I.: Anaemia in Pregnancy in Calcutta: Analysis of Haematological and Other Data from Five Hundred and Twenty-Nine Pregnant Women, Indian M. Research Mem., 1941, no. 33, p. 1.

99. Davidson, L. S. P.; Davis, L. J., and Innes, J.: Megaloblastic Anaemia of Pregnancy and the Puerperium, Brit. M. J. **2**:31, 1942.

100. Mudaliar, A. L., and Menon, M. K. K.: The Macrocytic Anaemia of Pregnancy, J. Obst. & Gynaec. Brit. Emp. **49**:284, 1942.

to any form of therapy except transfusion of blood and termination of the pregnancy. The authors report that in pregnancy the microcytic hypochromic type of anemia may develop into the macrocytic type with a high color index during treatment with iron compounds. In the treatment of anemia of pregnancy as observed in India, they found the combined administration of medicinal iron and liver extract to be of greatest value. Thirty of the patients in this series were observed for two to three months after delivery, and all exhibited normal hematologic values. Mudaliar and Menon see a resemblance between the macrocytic anemia of pregnancy and preeclamptic toxemia. In many of their patients diarrhea preceded the severe symptoms of anemia. In some instances ancylostomiasis may have been an etiologic factor.

A case of macrocytic anemia in pregnancy associated with preeclamptic toxemia is reported by Procopie and Armington.[101] The anemia was attributed to defective diet with hyperemesis and disturbance of gastric secretion. Improvement followed administration of liver extract.

The construction of diets to meet the needs of women during pregnancy and lactation is outlined by Bethell and Blecha.[102] In a study of the nutritional and the hematologic status of 495 women residing in rural areas of Michigan a positive correlation was found between dietary deficiency of iron and hypochromic anemia, and between inadequate intake of protein from animal sources and macrocytic anemia.

On the African Gold Coast over a ten year period macrocytic anemia occurred in 100 hospitalized pregnant women, approximating 1 per cent of the total number of such women, according to Russell.[103] Sixty-four of the subjects were primiparas. In 29 of the women the anemia occurred before the twenty-eighth week of gestation. The incidence of malaria, 29 per cent, and that of a positive Wassermann reaction were about the same in the group with anemia as in the population in general. In most of the patients the anemia was severe, but they responded well to liver extract therapy, and spontaneous recovery usually followed termination of the pregnancy. The author reports that discontinuance of liver therapy after remission had been induced was not followed by recurrence of anemia during the same pregnancy but that often the anemia reappeared during subsequent pregnancies. If the macrocytic anemia remains untreated, the prognosis is poor. The mortality of hospitalized patients with macrocytic anemia was 5 per cent. The author believes that the causation of the macrocytic anemia observed on the Gold Coast is complex and varied. The most important factors, in order of probability were: dietary deficiency, especially of the "extrinsic factor" of Castle; disturbance of gastric secretion; intercurrent disease, such as malaria, and preexisting anemia from deficiency of iron.

The case of a 29 year old multipara, born in Ireland, who was first observed just before the termination of pregnancy, is reported by Daniel and Antis.[104] The erythrocyte count was 860,000 per cubic millimeter; the hematocrit reading was 12 per cent and the hemoglobin value 18 per cent. Because of persistent nausea and vomiting, her diet had been greatly restricted since the second month of gestation. Free hydrochloric acid was present in the gastric contents. The patient

101. Procopie, G., and Armington, C.: Pregnancy Complicated by Preeclamptic Toxemia and Pernicious Anemia, J. Indiana M. A. **35**:466, 1942.

102. Bethell, F. H., and Blecha, E.: The Diet in Pregnancy, Clinics **1**:346, 1942.

103. Russell, B. A. S.: Macrocytic Anaemia in Pregnant Women on Gold Coast, Lancet **2**:792, 1941.

104. Daniel, M., and Antis, M.: Macrocytic Hyperchromic Anemia of Pregnancy, Am. J. Obst. & Gynec. **44**:93, 1942.

responded to transfusion of blood and parenteral injection of liver and was delivered spontaneously of a full term living child.

Nineteen cases of severe anemia associated with pregnancy or the puerperium are reported by Lescher.[105] Nine of the women had "pernicious anemia of pregnancy" and hemolytic anemia of the Lederer type, characterized by an abrupt onset. The patients in the former group were chiefly in the middle and later years of the reproductive period, and the condition developed insidiously during the last trimester of gestation. The changes in the quantitative and morphologic characteristics of the blood were similar to those observed in true pernicious anemia, but macrocytosis was less marked, and leukopenia was absent. In none of the patients were there signs referable to changes in the central nervous system; and in all there occurred a prompt response to liver therapy. In the group characterized by hemolytic anemia, the rapid lowering of the blood values was not associated with spherocytosis or with increased fragility of the erythrocytes. Reticulocytosis and bilirubinemia were present. The anemia failed to respond to liver therapy, but the condition was often completely relieved by blood transfusion.

The case of a 27 year old typist who presented the features of aplastic anemia at the fourth month of gestation is reported by Hurwitt and Field.[106] Hemorrhagic manifestations predominated, all of the cellular elements arising from the marrow were reduced in number, and at necropsy the diagnosis was confirmed. The authors review the literature on the subject, and find evidence that the association of aplastic anemia and pregnancy may be more than coincidental. In such cases they advise termination of the pregnancy whenever this is feasible. Stodtmeister and Büchmann[107] report a case of aplastic anemia in a woman of 41 years who was first seen twelve days after she had given birth to a full term healthy infant. There was a history of progressive weakness and increasing edema throughout the last two months of gestation. The erythrocyte count was said to be 300,000 per cubic millimeter and the hemoglobin value 10 per cent. The leukocyte count was 14,200 per cubic millimeter with a neutrophil percentage of 79. The platelet values were not abnormal. Free acid was present in the gastric contents. No response was observed following parenteral injection of a product corresponding to a purified solution of liver U. S. P., but the patient recovered after blood transfusions. Aspirated sternal marrow revealed a selective absence of maturation of erythrocytic elements. The authors draw an analogy between such inhibition of erythropoiesis leading to "acute aplastic anemia" and a similar arrest of granulocyte or platelet development giving rise, respectively, to agranulocytosis and thrombocytopenic purpura.

The hemoglobin levels and the incidence of febrile puerperal morbidity among 1,001 multiparas were correlated by Bickerstaff.[108] He found an almost uninterrupted decline in the incidence of febrile morbidity with increasing values of hemoglobin, the relationship persisting until the hemoglobin level approached 12 Gm. per hundred cubic centimeters. Excessive loss of blood at parturition was also related to the incidence of fever, but unless the hemorrhage was of a serious degree, the occurrence of fever was more closely related to the hemoglobin

105. Lescher, F. G.: Grave Anaemias in Pregnancy and the Puerperium: Report of Seventeen Cases, Lancet **2**:148, 1942.

106. Hurwitt, E. S., and Field, L.: Aplastic Anemia in Pregnancy, Am. J. Obst. & Gynec. **43**:42, 1942.

107. Stodtmeister, R., and Büchmann, P.: Ueber aplastischanämische Krise in der Schwangerschaft, Klin. Wchnschr. **21**:701, 1942.

108. Bickerstaff, H. J.: Relationship Between Late Prenatal Hemoglobin Levels and Febrile Puerperal Morbidity, Am. J. Obst. & Gynec. **43**:997, 1942.

value before delivery than to the quantity of blood subsequently lost. The author also states that "the low prenatal blood values prevailing among negroes on this service are an important factor contributing to their much greater incidence of puerperal morbidity."

Evidence concerning the rate of transmission of iron from the maternal alimentary tract to the blood of the human fetus was obtained by Pommerenke and his co-workers.[109] They fed single doses of iron containing the radioactive isotope to pregnant women shortly before delivery or before therapeutic abortion. The radioactive iron was detected in the fetal circulation in as short a time as forty minutes after its ingestion by the mother. The authors therefore conclude that the plasma rather than the erythrocytes, which would have to undergo preliminary disintegration, must be the vehicle for the transmission of iron from the mother to the fetus. In the fetal tissues there was wide dissemination of radioactive iron, with the largest portion present in the erythrocytes and the next largest in the liver.

Mineral Metabolism and Experimental Anemia.—The phosphorus content of the whole blood and of the erythrocytes of 7 anemic children was determined by Behrendt.[110] In 5 children the anemia was of the hypochromic variety, while in 2 the blood picture was characterized by a color index greater than 1. No correlation was observed between the retention of phosphorus by the red cells and the presence of any kind of pathologic blood cells or any special type of anemia.

In order to determine the effect of a high fat intake on the rate of destruction of erythrocytes as measured by the excretion of urobilin, Josephs and his associates[111] fed 6 normal infants between 5 and 8 months of age on diets which derived from 35 to 85 per cent of their caloric value from fats. They found an increase of the fecal output of urobilin during the period of these diets, an increase independent of the type of fat. Free fatty acids and soaps exerted a similar effect, suggestive of increased hemolysis. There was also an abrupt but temporary rise in the excretion of iron, which suggested to the authors that there may have been either a "washing out" of iron from storage depots or an excessive output of hemoglobin which was later counterbalanced by increased production of hemoglobin. They are of the opinion that the hemolytic action of fats is probably due to the formation and absorption of soaps or fatty acids. In the healthy infants studied the hemolytic effect was insufficient to produce anemia or a rise in reticulocytes, but the authors suggest that when the bone marrow is already being subjected to strain, such a diet may aggravate the situation.

Studies of the iron balance of 66 young women between the ages of 16 and 27 years who were subsisting on self-chosen diets were undertaken by Leverton and Marsh.[112] Observations were carried out during ninety-nine one week periods. The average daily intake of iron provided an average daily storage of 1.37 mg., which was considered ample for replacement of normal menstrual losses. The authors state that diets optimum in other essential foods appear to influence favorably the absorption of iron.

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109. Pommerenke, W. T.; Hahn, P. F.; Bale, W. F., and Balfour, W. M.: Transmission of Radioactive Iron to the Human Fetus, Am. J. Physiol. **137**:164, 1942.

110. Behrendt, H.: Studies on Blood Phosphorus: Intracellular and Extracellular Blood Phosphorus in Anemia in Children and in Experimental Anemia, Am. J. Dis. Child. **64**: 789 (July) 1942.

111. Josephs, H. W.; Holt, L. E., Jr.; Tidwell, H. C., and Kajdi, C.: Influence of Dietary Fat upon Excretion of Urobilin, Bull. Johns Hopkins Hosp. **71**:84, 1942.

112. Leverton, R. M., and Marsh, A. G.: The Iron Metabolism and Requirement of Young Women, J. Nutrition **23**:229, 1942.

Black and Powell [113] gave 1 liter of blood by duodenal tube to each of 2 patients with iron deficiency anemia associated with achlorhydria and to a normal person with abundant secretion of hydrochloric acid. From 10 to 25 per cent of the iron contained in the ingested blood was not recovered in the feces, although a larger amount was excreted by the healthy subject. Of the iron which was apparently absorbed, some but not all could be accounted for as "easily split-off" iron (Barkan). The remainder must have been derived from hemoglobin, which indicates that, contrary to earlier reports, in the alimentary tract the hemoglobin molecule may be decomposed, with release of an absorbable iron compound, even in the presence of achlorhydria.

The iron and the copper contents of the livers, spleens, stomachs and, when present, tumor tissue of 15 control subjects, 23 patients with cancer plus anemia and 11 patients with noncancerous diseases plus correspondingly severe anemia were determined by Gross, Sandberg and Holly.[114] There was abundant storage of iron and copper in the livers and spleens of many patients with cancer, and the level of storage bore no relation to the incidence or the severity of anemia. There were normal or greater than normal amounts of iron and copper in the stomachs of such patients, so that the hypochromic anemia could not be accounted for by inadequate stores of these metals. The tumor tissue itself showed marked affinity for copper.

The hypochromic iron deficiency anemia induced in adult dogs by repeated venesection failed to respond to the administration of iron and copper salts when high levels of cobalt were added to the diet, according to McKibbin and his co-workers.[115] Rapid regeneration of hemoglobin occurred, however, when the ration was further supplemented with dry whole liver or liver extracts. The authors report that synthetic B vitamins, bile salts, cysteine, uropterin concentrates and large doses of iron when fed individually failed to exhibit the activity of liver preparations but that when all of these supplements were administered collectively, regeneration of blood occurred comparable to that induced with liver preparations. However, in animals fed the mixture of pure supplements the blood plasma iron was not mobilized, as it always is during liver therapy. They also found that when dogs with chronic anemia due to withdrawal of blood were fed a highly purified ration supplemented only with synthetic vitamins they retained their ability to regenerate hemoglobin and erythrocytes and that recovery was complete in two weeks after discontinuance of phlebotomy.

The blood volume of the dog is constant, in spite of varying degrees of anemia, according to Hahn, Bale and Balfour,[116] whose studies were based on the use of radioactive iron. They found that deficits in erythrocytes were compensated for by corresponding increases in plasma volume and that radioactive iron contained within circulating red cells was reutilized promptly in the formation of new erythrocytes after the physiologic destruction of the older forms. In another

113. Black, D. A. K., and Powell, J. F.: Absorption of Haemoglobin Iron, Biochem. J. **36**:110, 1942.

114. Gross, H.; Sandberg, M., and Holly, O. M.: Changes in Copper and Iron Retention in Chronic Diseases Accompanied by Secondary Anemia: Changes in Liver, Spleen and Stomach, Am. J. M. Sc. **204**:201, 1942.

115. McKibbin, J. M.; Schaefer, A. E.; Elvehjem, C. A., and Hart, E. B.: Studies on Hemorrhagic Anemia in Dogs, J. Biol. Chem. **145**:107, 1942.

116. Hahn, P. F.; Bale, W. F., and Balfour, W. M.: Radioactive Iron Used to Study Red Blood Cells over Long Periods: The Constancy of the Total Blood Volume in Dog, Am. J. Physiol. **135**:600, 1942.

article Hahn and his associates [117a] report that values for the total erythrocyte volumes of normal and anemic dogs when determined either by viviperfusion [117b] or by the use of "radioactive iron tagged red cells" were from 10 to 40 per cent lower than the values obtained by simultaneous hematocrit and plasma volume determinations. They state that because of the relatively stationary plasma film next to the walls of the vessels the hematocrit value of the entire vascular system is considerably below that of the large vessels and that the cell plasma ratio of the smaller vessels is still lower. In the dog they found no evidence of considerable stores of immobilized red cells. The "rapidly circulating blood volume" obtained by dividing the erythrocyte volume as measured by the radioactive iron method by the venous hematocrit value was found to be considerably less than the total blood volume. The "rapidly circulating blood plasma" amounts to about 80 per cent of the total blood plasma.

A number of other studies dealing with mineral metabolism and factors in the production of hemoglobin in experimental and clinical anemic states have been published by the group in Rochester, N. Y., working under the direction of G. H. Whipple. Balfour and his associates [118] studied the absorption of iron by means of its radioactive isotope in 34 patients with a variety of clinical conditions. The absorption was increased in pregnancy but not in pernicious anemia, hemochromatosis, familial icterus, erythroblastic anemia, leukemia, chronic infections and polycythemia. They believe that the absorption of iron is governed by the reserve stores of iron in the body rather than by the presence of anemia and that "this control is exerted upon the gastro-intestinal mucosa which can refuse or accept iron under various conditions."

Cruz, Hahn and Bale [119] produced acute destruction of red cells by administering acetylphenylhydrazine to iron-depleted dogs and to others with adequate or excessive iron stores. Previously, radioactive iron had been introduced into the erythrocytes by oral administration over a twenty-day period. The radioactive iron was detected and measured in the new erythrocytes formed in response to the hemolysis within a few days and as soon as there was evidence of regeneration. This occurred in all the dogs, irrespective of depletion or of excess storage of iron and indicated that the greater part of the iron utilized in the synthesis of hemoglobin is derived directly from disintegrated erythrocytes rather than from storage reserves. According to Cruz, Hawkins and Whipple,[120] healthy, nonanemic dogs in which bile fistulas have been produced excrete hemoglobin pigment almost quantitatively after either the administration of acetylphenylhydrazine or the intravenous injection of hemoglobin, but the animals' capacity to form new hemoglobin remains unimpaired and the regeneration is not affected significantly by the constituents of the diet.

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117. (*a*) Hahn, P. F., and others: Red Cell and Plasma Volumes (Circulating and Total), as Determined by Radio Iron and by Dye, J. Exper. Med. **75**:221, 1942. (*b*) Whipple, G. H.: Hemoglobin of Striated Muscle: Variations Due to Age and Exercise, Am. J. Physiol. **76**:693, 1926.

118. Balfour, W. M., and others: Radioactive Iron Absorption in Clinical Conditions: Normal, Pregnancy, Anemia, and Hemochromatosis, J. Exper. Med. **76**:15, 1942.

119. Cruz, W. O.; Hahn, P. F., and Bale, W. F.: Hemoglobin Radioactive Iron Liberated by Erythrocyte Destruction (Acetyl Phenylhydrazine), Promptly Reutilized to Form New Hemoglobin, Am. J. Physiol. **135**:595, 1942.

120. Cruz, W. O.; Hawkins, W. B., and Whipple, G. H.: Acetyl Phenylhydrazine Anemia; Bile Pigment Elimination and New Hemoglobin Reconstruction in Bile Fistula Dog, Am. J. M. Sc. **203**:848, 1942.

Yoshikawa, Hahn and Bale [121] found that "following the ingestion of radioactive copper by the dog, the metal appears quickly in the plasma, the concentration reaching its peak in from two to five hours, after which it falls abruptly." The copper also appears in the circulating erythrocytes, and the authors' data suggest that in dogs in which regeneration of erythrocytes is accelerated, because of previous hemorrhage, the uptake of copper is somewhat more extensive than it is in nonanemic animals. This effect, however, may be due to greater absorption of copper by the newly formed red cells.

In stimulating the production of hemoglobin in anemic dogs Robscheit-Robbins and Whipple [122] found the action of copper variable. In some instances copper enhanced the effect of iron, but in others regeneration was slowed. The diets were not deficient in copper, and the hepatic and the splenic tissue of the anemic animals contained more of the metal than is present in the organs of normal dogs. The authors suggest that copper may exert an effect on enzyme complexes related to the production of globin and hemoglobin. When cobalt was administered to dogs, no tendency toward polycythemia was observed, but the ingestion of more than minimal amounts of cobalt exerted an inhibitory effect on the formation of hemoglobin in response to administration of iron.

Whipple and Robscheit-Robbins [123] measured the hemoglobin-producing factors contained in human livers (obtained at necropsy from patients with various clinical conditions) by administering such material to dogs rendered anemic by repeated bleeding. It was found that in pernicious anemia in relapse and in aplastic anemia large stores of such factors were present. Following liver therapy the values in pernicious anemia were reduced. Conditions associated with "secondary" anemia were characterized by low or low normal values as determined by the production of hemoglobin. In polycythemia, hypoproteinemia, pregnancy with and without eclampsia, and lactation the values were abnormally low, whereas in hemochromatosis, erythroblastic anemia and hemolytic icterus the values were within or close to the normal range. A wide range of results was obtained in connection with leukemia. A general discussion of the role of amino acids in the formation of hemoglobin based largely on previously reported work, was published by Robscheit-Robbins.[124]

Administration of a single therapeutic dose of copper containing the radioactive isotope, $_{29}Cu^{64}$, obtained by bombardment of nickel, resulted in greater retention of the metal by copper-deficient rats than by iron-deficient animals, according to Schultze and Simmons.[125] In both groups only a small fraction of the copper fed was retained. Within twenty-four to forty-eight hours after ingestion the greatest deposition of copper was found in kidney, liver and marrow, in that order.

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121. Yoshikawa, H.; Hahn, P. F., and Bale, W. F.: Red Cell and Plasma Radioactive Copper in Normal and Anemic Dogs, J. Exper. Med. **75**:489, 1942.

122. Robscheit-Robbins, F. S., and Whipple, G. H.: Copper and Cobalt: Related Hemoglobin Production in Experimental Anemia, J. Exper. Med. **75**:481, 1942.

123. Whipple, G. H., and Robscheit-Robbins, F. S.: Hemoglobin Production Factors in the Human Liver: Anemias, Hypoproteinemia, Cirrhosis, Pigment Abnormalities and Pregnancy, J. Exper. Med. **76**:283, 1942.

124. Robscheit-Robbins, F. S.: Amino Acids in Hemoglobin Formation, Federation Proc. **1**:219, 1942.

125. Schultze, M. O., and Simmons, S. J.: Use of Radioactive Copper in Studies on Nutritional Anemia of Rats, J. Biol. Chem. **142**:97, 1942.

Iron in the form of chelidamate complexes was administered parenterally to rats and rabbits by Brownlee, Bainbridge and Thorp.[126] These preparations were shown to be rapidly transported to the liver, the spleen and the kidneys and to be outstanding as factors in the production of hemoglobin by iron-deficient animals. After parenteral injection none of the iron was excreted by the intestine. They found that injected iron was exceedingly toxic to rats with hypochromic anemia.

To rats who had been made severely anemic by means of an exclusive milk diet Freeman and Ivy [127] fed supplements of iron, copper and manganese, and to different groups various antacids were given. They found that the retention of iron by these animals was greatly reduced when either calcium carbonate or aluminum hydroxide was given. Magnesium trisilicate caused a reduction in retention of iron, but to a degree of questionable significance. Aluminum phosphate had no effect on the retention of iron. The determinations were made by ashing the animal carcasses entire. The conclusion is drawn that the intake of iron should be increased in cases in which there is consumption of aluminum hydroxide or calcium carbonate.

György [128] and his co-workers found that crude linoleic acid fed with or without butter yellow in a synthetic diet was toxic to rats and led to progressive hypochromic anemia with leukopenia and loss of weight. The effects of linoleic acid were neutralized by administration of yeast. According to Harrison,[129] rats made anemic by means of a milk diet responded slightly less well to iron and copper supplements when phytic acid was included in their diets. This study was motivated by the observation, made previously, that phytic acid contributes to the production of rickets in rats by precipitating dietary calcium, and it was thought that a similar effect might be exerted on ingested iron.

The concentration of copper in the blood of sheep and cows was determined by Beck.[130] He found no absolute correlation between the values obtained and the development of anemia, but he states that anemia generally occurs if the copper level of the blood falls below 0.1 to 0.2 mg. per liter for any length of time. Sudden death, the "falling disease," is a not infrequent occurrence among cattle in certain areas of Australia. Bennetts, Harley and Evans [131] have demonstrated quite conclusively that the death of these animals is due to severe anemia consequent on deficiency of copper. Necropsy revealed atrophy and fibrosis of the heart similar to the starvation atrophy of the myocardium observed in human beings and death is attributed presumptively to either ventricular fibrillation or heart block. It is suggested that copper may be necessary to the oxidation-reduction enzyme systems of bovine cells. The tendency of the disorder to be manifest in the spring is believed to be due to the special stress and strain incident to this season, including rapid increase in weight, pregnancy and parturition.

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126. Brownlee, G.; Bainbridge, H. W., and Thorp, R. H.: The Pharmacology of Iron in Parenteral Treatment, Quart. J. Pharm. & Pharmacol. **15**:148, 1942.

127. Freeman, S., and Ivy, A. C.: The Influence of Antacids upon Iron Retention by the Anemic Rat, Am. J. Physiol. **137**:706, 1942.

128. György, P.; Tomarelli, R.; Ostergard, R. P., and Brown, J. B.: Unsaturated Fatty Acids in Dietary Destruction of N, N-Dimethylaminoazobenzene (Butter Yellow) and in the Production of Anemia in Rats, J. Exper. Med. **76**:413, 1942.

129. Harrison, D. C.: Phytic Acid in Anaemia, Irish J. M. Sc., 1942, no. 201, p. 540.

130. Beck, A. B.: Studies on Blood Copper of Sheep and Cows, Australian J. Exper. Biol. & M. Sc. **19**:249, 1941.

131. Bennetts, H. W.; Harley, R., and Evans, S. T.: Studies on Copper Deficiency of Cattle: The Fatal Termination ("Falling Disease"), Australian Vet. J. **18**:50, 1942.

HEMOLYTIC AND ERYTHROBLASTIC ANEMIAS

Congenital and Acquired Types.—The hemolytic syndromes are discussed, with a review of the recent literature on the subject, by Dameshek,[132] who gives the following classification of these disorders:

A. Hemoglobinurias (exceedingly rapid hemolysis, with hemoglobinemia and hemoglobinuria).
   1. Paroxysmal cold
   2. Paroxysmal nocturnal
   3. March
   4. Favism
   5. Unclassified types

B. Hemolytic anemias.
   1. Hereditary
      a. Spherocytic
      b. Target cell (Mediterranean)
      c. Sickle cell (African)
   2. Acquired (acute, subacute and chronic types)
      a. Chemical, including the sulfonamide drugs
      b. Immune body (hemolysins and agglutinins), including erythroblastosis foetalis
      c. Idiopathic, including hypersplenic types
      d. Symptomatic

A hemolytic index has been devised by Miller, Singer and Dameshek [133] which expresses the daily fecal output of urobilinogen per hundred grams of circulating hemoglobin. This value is obtained by the calculation:

$$\frac{\text{Average (of 4 days) daily output of fecal urobilinogen (mg.)} \times 100}{\text{Total hemoglobin (hemoglobin in Gm. per 100 cc.} \times \frac{\text{total blood volume}}{100}}$$

Normal values for the hemolytic index range between 11.1 and 20.8. The values are increased in cases of hemolytic anemia, pernicious anemia, Cooley's anemia and, to some extent, Gaucher's disease. The values are below normal in cases of anemia due to deficiency of iron and cases of polycythemia and after splenectomy for any condition.

A family of which several members were afflicted with congenital hemolytic jaundice has been reported by Cooper [134] from Melbourne, Australia. The interesting feature of these patients was their similarity in many respects to patients with Cooley's erythroblastic anemia. The mongoloid facies was present, and there were extensive and characteristic changes in the bones of the vault of the skull. The author discusses the relationship of congenital hemolytic jaundice, sickle cell anemia and erythroblastic anemia. Three cases of chronic familial hemolytic anemia in which an erythroblastic reaction, manifest in the circulating blood, followed splenectomy are reported by Stransky and Regala.[135] One of the patients was a man of 23 years, in whom the erythroblastosis persisted for only a few days and was followed by the appearance of Howell-Jolly bodies and a rapid increase in erythrocytes. Two of the patients were girls 6 and 8 years old, with family

132. Dameshek, W.: Hematology: Anemia, with Particular Reference to the Hemolytic Syndrome, New England J. Med. **226**:339, 1942.

133. Miller, E. B.; Singer, K., and Dameshek, W.: The Use of the Daily Fecal Output of Urobilinogen and the Hemolytic Index in the Measurement of Hemolysis, Arch. Int. Med. **70**:722 (Nov.) 1942.

134. Cooper, E. L.: Familial Acholuric Jaundice Associated with Bone Changes, Ann. Int. Med. **15**:858, 1941.

135. Stransky, E., and Regala, A. C.: Erythroblastic Anemia Following Splenectomy in Cases of Chronic Familial Hemolytic Anemia, Am. J. Dis. Child. **63**:859 (May) 1942.

histories of jaundice and anemia, who exhibited lasting erythroblastosis after splenectomy with no improvement in their anemia but with cessation of hemoclastic crises. In all 3 cases the erythrocytes were of normal fragility, and in no case was spherocytosis observed. Five cases of hemolytic anemia, apparently not of the familial or spherocytic type, are reported by Sharpe and Tollman.[136] No cause for the hemolysis was discovered in any of these cases, and splenectomy was followed by slight improvement but no real cure. Hyperplasia of reticulum cells and phagocytosis of pigment were observed in the spleens; otherwise there were no definite pathologic changes.

A case of hemolytic anemia due to the presence of autoagglutinins and hemolysins is reported by Reisner and Kalkstein,[137] who point out that autoagglutinins are actually panagglutinins in that they act not only on the subject's red cells but on the erythrocytes of all other persons. The phenomenon is a true antibody reaction, and absorption of the antibody by the red cells can be demonstrated. The agglutination is usually accelerated by cold and retarded by heat, but in the case reported the reaction persisted in spite of warming to 37 C. (98.6 F.). The agglutinin could not be separated from the erythrocytes. Improvement followed splenectomy, and transfusions, which previously had been followed by severe hemolytic reactions, were tolerated after the operation, with resulting rise in the red cell count. The antibodies, however, persisted in the plasma, but presumably in insufficient concentration to produce an in vivo reaction. The death of this patient occurred on the ninth day after operation, apparently from exsanguination into the gastrointestinal tract. Necropsy was not performed.

The case of a man 41 years old with Gaucher's disease associated with severe hemolytic anemia is reported by Mandelbaum, Berger and Lederer.[138] The erythrocytes were not deficient in resistance to hypotonic salt solution, but occasional microspherocytes were seen. Splenectomy was followed by decided and continued improvement. Brewster and Wollenman[139] observed a patient with myeloid metaplasia of the spleen accompanied by acute hemolytic anemia. No extrinsic or intrinsic etiologic factors which might have accounted for the increased destruction of blood were discovered. There was increased fragility of the red cells, but the disease underwent exacerbation after splenectomy and terminated fatally. Pathologic evidence suggested that the spleen of this patient was an important blood-forming organ.

The literature on the familial anomaly of erythrocytes known as elliptocytosis is reviewed by Cooley.[140] Sixty-four families containing 246 affected persons have been reported. Of the affected ones, about 15 per cent were anemic. The fragility test was performed in two thirds of the cases, and decreased and normal resistance were observed in about equal numbers of cases. The author states that the erythrocytes do not acquire the characteristic oval form until they leave the reticulocyte stage of development. According to him, transfusion experiments indicate that cells of this type live only about half as long in the circulation as normal cells. Cooley's own patients with elliptocytosis all showed anemia,

136. Sharpe, J. C., and Tollman, J. P.: Refractory Hemolytic Anemia: A Report of Five Cases in Which Treatment Was with Splenectomy, Arch. Int. Med. **70**:11 (July) 1942.

137. Reisner, E. H., Jr., and Kalkstein, M.: Autohemolysinic Anemia with Auto-Agglutination: Improvement After Splenectomy, Am. J. M. Sc. **203**:313, 1942.

138. Mandelbaum, H.; Berger, L., and Lederer, M.: Gaucher's Disease: A Case with Hemolytic Anemia and Marked Thrombopenia: Improvement After Removal of Spleen Weighing 6,822 Grams, Ann. Int. Med. **16**:438, 1942.

139. Brewster, H. H., and Wollenman, O. J., Jr.: Myeloid Metaplasia of the Spleen with Acute Hemolytic Anemia: Report of a Case, New England J. Med. **227**:822, 1942.

140. Cooley, T. B.: Elliptocytosis and Anemia, Am. J. Dis. Child. **64**:190 (July) 1942.

which was to be expected, since they were referred to him for that reason, and all were males, which was unexpected, since the trait is inherited as a mendelian dominant. Lasting relief from the anemia may follow blood transfusions.

The subject of Mediterranean anemia is reviewed by M. L. Goldhamer,[141] who reports 12 cases in a family of Italian origin, the patients representing three generations. Among them, features definitely indicative and features suggestive of Mediterranean anemia were observed. The presence of "target" cells and the increased resistance of the erythrocytes to hypotonic salt solution were cardinal characteristics. No form of therapy employed was of specific value, including administration of medicinal iron and liver preparations and maintenance on diets high in protein and vitamins.

Familial nonhemolytic jaundice, although not a disorder affecting the corpuscular elements of the blood, is properly considered in conjunction with the hemolytic anemias because of the likelihood of its being confused with them. An instance of this disease in an Irishman of 50 years is reported by Curry, Greenwalt and Tat.[142] The patient had been jaundiced since birth. He presented no evidence of disease of the liver or of the spleen and no anemia or reticulocytosis. The output of fecal urobilinogen was low, and the urinary urobilinogen was normal. Splenectomy, performed some years before, had been without effect on the jaundice. Biopsy of the liver revealed no pathologic change, and the results of tests of hepatic function were normal. The blood bilirubin level was elevated, the urine was free from bile, and the ingestion of sodium dehydrocholate was not followed by an increase in fecal urobilinogen. The patient's sister, aged 54, suffered from the same disorder.

The Marchiafava-Micheli syndrome is defined by Dameshek[143] as "chronic hemolytic jaundice with paroxysmal nocturnal hemoglobinuria and perpetual hemosiderinuria." Two cases are reported. One of the patients was a woman of 20 years, one of identical twins whose twin was not affected, and the other was a man of 23 years on whom splenectomy had been performed fourteen months before. This disease is characterized by either an abrupt or a gradual onset due to unknown factors and by the development of a specific and peculiar type of hemolytic antibody to which the red blood cells are sensitized. The cells are unusually susceptible to acid hemolysis. Greatly increased destruction of blood occurs with unusually marked and chiefly nocturnal hemoglobinemia and hemoglobinuria. There is also persistent hemosiderinuria, and both the hemoglobinuria and the hemosiderinuria are apparently mediated through the kidney. According to the author, this disease should be thought of in all cases of obscure hemolytic anemia, and in such cases the acid fragility test and an examination for hemosiderin should be done. The prognosis of paroxysmal nocturnal hemoglobinuria is unfavorable, and deposition of hemosiderin in the kidney frequently leads to impairment of renal function.

Four cases of hemoglobinuria occurring in boys, 3 of whom were of Jewish extraction, are reported by Acuña and Gambirassi.[144] The ages of the subjects

141. Goldhamer, M. L.: Mediterranean Anemia in the Adult (A Family History Analysis), Ohio State M. J. **38**:321, 1942.

142. Curry, J. J.; Greenwalt, T. J., and Tat, R. J.: Familial Non-Hemolytic Jaundice: Report of a Case with Liver Biopsy, New England J. Med. **226**:909, 1942.

143. Dameshek, W.: Paroxysmal Nocturnal Hemoglobinuria; Marchiafava-Micheli Syndrome, Bull. New England M. Center **4**:224, 1942.

144. Acuña, M., and Gambirassi, A. C.: A próposito de algunos casos de hemoglobinuria con síndrome anemoictérico agudo, grave (anemia hemolítica, de Lederer), Arch. argent. de pediat. **17**:421, 1942.

ranged from 19 months to 3½ years. The clinical picture consisted of a sudden onset of fever, hemoglobinuria, splenomegaly, anemia, jaundice and a rapid course terminating in death of 2 of the 4 children. There was no family history of a similar illness or of another form of blood dyscrasia in any of these patients. One of the patients who succumbed to the disease had had measles fifteen days previously. The authors discuss the causes of hemoglobinuria and hemoglobinemia as seen in infancy and state that these conditions may be associated with a variety of processes, including intoxications from chlorates, sulfanilamide and its derivatives, hydrogen sulfide, arsines, snake venoms, mushroom poisons, spider bites and severe burns. Among infectious agents responsible for acute hemolysis are mentioned scarlet fever, typhoid fever, diphtheria, pneumococcic infections, measles, erysipelas and malaria. Rather surprisingly, the authors fail to refer to sensitization to the protein of foods or inhalants as the mechanism responsible for this syndrome in some instances. Three other types of pathologic process are considered in the differential diagnosis of the cases reported. They are paroxysmal hemoglobinuria, acute hemolytic anemia of Lederer and the hemolytic crises of congenital hemolytic jaundice. The characteristic features of each of these conditions are described. The cases reported appear to fall in the second group, although the agents responsible for the acute hemolysis remain obscure.

With reference to a discussion of march hemoglobinuria, Comerford [145] in a letter to the editor of the *British Medical Journal* describes his own case observed in the 1880's after long distance running. He stated that his trainer regarded the passage of "port wine colored" urine as a common phenomenon among participants in this type of sport.

The behavior of erythrocytes obtained from normal subjects and from patients with a variety of clinical diseases in response to the hemolytic action of saponin, sodium carbonate, sodium oleate, ethyl alcohol and hypotonic sodium chloride solutions was determined by Wieczorowski and Fishback.[146] No changes of diagnostic value were found.

By intravenous injections of rattlesnake venom Bethell and Bleyl [147] were able to induce in dogs, rabbits and a monkey microspherocytosis, reticulocytosis, anemia and increased fragility of erythrocytes. After a number of these injections the animals became refractory to the action of the venom and the blood values returned to normal. The refractory period persisted for about two weeks after discontinuance of the injections. Splenectomy, although followed by morphologic changes in the circulating blood, did not affect the response of the animals to subsequent injections of venom.

A case of acute hemolytic anemia following administration of phenothiazine (anthelminthic) is reported by Johnstone.[148] He states that of 58 cases in which this drug was used, some form of toxic reaction severe enough to require treatment has occurred in 8. According to Collier and Allen,[149] phenothiazine in vitro

145. Comerford, B. H.: March Haemoglobinuria, Brit. M. J. **1**:774, 1942.

146. Wieczorowski, E., and Fishback, H. R.: A Study of Type Hemolytic Reactions of Human Red Blood Cells in Disease, J. Lab. & Clin. Med. **27**:542, 1942.

147. Bethell, F. H., and Bleyl, K.: The Production of Microspherocytosis of Red Cells and Hemolytic Anemia by the Injection of Rattlesnake Crotalus atrox Venom, J. Clin. Investigation **21**:641, 1942.

148. Johnstone, R. D. C.: Acute Haemolytic Anaemia Following Phenothiazine Therapy, Brit. M. J. **1**:259, 1942.

149. Collier, H. B., and Allen, D. E.: The Haemolytic Action of Phenothiazine Derivatives, Canad. J. Research **20**:283, 1942.

appears to act as an accelerator of hemolysis induced by either saponin or lysolecithin.

Hemolytic Anemia Produced by Sulfanilamide and Its Derivatives.—An instance of acute hemolytic anemia occurring during administration of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) is reported by Trier,[150] who analyzes the data supplied by about 90 cases of anemia attributed to the action of sulfanilamide and its derivatives, including sulfapyridine and sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole). Three fatalities are included in this series. The anemia is characterized by an abrupt onset, usually occurring between the third and the fifth day of administration of the drug, with rapid fall in the erythrocyte and hemoglobin values, jaundice, urobilinuria, leukocytosis and reticulocytosis. In the cases in which the intoxication is severe, hemoglobinemia, hemoglobinuria and enlargement of the liver are observed. The majority of persons who have had acute anemia from this cause will show recurrence on readministration of the same drug or another member of the sulfanilamide group.

Hendricks [151] reports that anemia of varying severity developed in 40 per cent of 433 patients who received one or more of the sulfanilamide derivatives. The incidence of anemia was about the same with sulfanilamide, sulfapyridine and sulfathiazole but was increased when more than one of these drugs were employed. Infants and children proved to be more susceptible than adults. Acute hemolytic anemia developed in 4.3 per cent of the patients, and was caused by each of the drugs employed, but most frequently by sulfanilamide or mixed therapy. The incidence of hemolytic anemia was almost three times as great in Negroes as in Caucasians. The onset of anemia was sometimes delayed for as long as ten to twelve days after the institution of therapy, and it did not appear to be dependent on the duration of treatment or on the concentration of the responsible drug in the blood.

A case of acute hemolytic anemia following administration of sulfathiazole is reported by Rothstein and Cohen.[152] Their patient, a man of 45 years, had lobar pneumonia caused by pneumococcus type VII. On the sixteenth day of the administration of the drug, hemoglobinuria, severe hemolytic anemia, a leukemoid reaction with a leukocyte count of 67,000 per cubic millimeter, autoagglutination of red cells, toxic hepatitis and signs of renal damage developed. Arrest of the hemolytic process and recovery from the anemia were relatively rapid following the institution of blood transfusion therapy, but evidence of hepatic and renal damage persisted for a long time. Bunim and Israel [153] report the case of a man of 38 years who received 18 Gm. of sulfathiazole over a period of eight days in treatment of cellulitis of the foot before development of jaundice, hemoglobinemia, hemoglobinuria, azotemia and impairment of renal function. Prompt recovery occurred after discontinuance of the drug and administration of blood by transfusion. Another case, reported by the same authors, was that of a man aged 52 who after receiving 16 Gm. of sulfathiazole during four days in treatment of

150. Trier, M.: Acute Hemolytic Anemia Developing During Therapy with Substances Belonging to the Sulfanilamide Group: Survey and Report of Case, Acta med. Scandinav. **108**:117, 1941.

151. Hendricks, C. B.: Sulfonamide Compounds: Blood Changes Therefrom, California & West. Med. **56**:253, 1942.

152. Rothstein, I., and Cohen, S.: Acute Hemolytic Anemia, Autoagglutination, Toxic Hepatitis and Renal Damage Following Sulfathiazole Therapy: Case Report, Ann. Int. Med. **16**:152, 1942.

153. Bunim, J. J., and Israel, M.: Acute Hemolytic Anemia Caused by Sulfathiazole, Ann. Int. Med. **16**:333, 1942.

lobar pneumonia showed acute hemolytic anemia. Hipsley [154] reports a case of severe hemolytic anemia in a girl of 3 years who received only 3 grains (0.19 Gm.) of sulfapyridine in treatment of acute tonsillitis and whose erythrocyte count twenty-four hours later was 1,430,000 per cubic millimeter. The patient recovered following transfusion therapy.

Foy and Lewis [155] studied the effect of blood transfusion in the hemolysis associated with blackwater fever and that caused by the administration of sulfanilamide or its derivatives. In neither of these hemolytic states did they find any evidence that blood transfusions aggravate the destruction of erythrocytes.

The effect of promin (a glucoside derivative of 4,4-diaminodiphenyl sulfone) on the blood was investigated by Hall and his associates.[156] This compound was administered in 70 cases of tuberculosis. In 64 of the cases the disease involved the lungs, and in the remainder it was a meningeal, renal or bone infection. The drug was usually given by mouth and thus administered it was much more toxic with respect to incidence and severity of hemolytic anemia than when given by a parenteral route. After daily doses of 3.2 Gm. had been given for a period of eight to ten days, hemolysis usually developed, accompanied by anemia, leukocytosis and thrombocytosis. When the doses given during the initial period of administration were relatively small, "tolerance" was sometimes acquired, which was interpreted as a state in which regeneration of erythrocytes was stimulated to such an extent that anemia either failed to develop or was minimal. On discontinuance of the medication the blood values returned promptly to normal, without evidence of residual harmful effects on the hemopoietic system. One of the patients had extremely severe anemia, with an erythrocyte count of 900,000 per cubic millimeter, after 1.6 Gm. of promin had been administered daily for three days. When the administration of the drug was discontinued, recovery was spontaneous.

Erythroblastosis Foetalis and Icterus Gravis Neonatorum.—In a pathologic study of erythroblastosis Javert [157] classifies 47 cases observed by him into five groups: (1) cases with hydrops, 16; (2) cases with icterus, 22; (3) cases with anemia, 3; (4) cases with hemorrhagic diathesis, 3; (5) cases without hydrops, icterus, anemia or hemorrhagic diathesis, 3. The mortality in these groups was, respectively, 100, 54, 33, 33 and 100 per cent. The total incidence of erythroblastosis was 1 case to every 438 newborn infants, and the condition was held responsible for 3.2 per cent of all fetal deaths. The author believes that dysfunction of the fetal liver plays an important part in the genesis of this disorder.

Five infants in whom erythroblastosis was the cause of death are the subject of an article by Follis, Jackson and Carnes.[158] Hydrops foetalis was present in 3 infants and icterus gravis with hemorrhagic diathesis in a fourth; the fifth child appeared to be normal, but at necropsy enlargement of the liver and of the spleen, with active erythropoiesis in these organs and in the kidneys, was observed. Particular emphasis was placed on the changes in the bones, of which the most

154. Hipsley, P. L.: Acute Hemolytic Anaemia Following Sulfonamide Therapy, M. J. Australia **1**:565, 1942.

155. Foy, H., and Lewis, E. G.: Blood Transfusion in Blackwater Fever and Haemolytic Anaemias Following Sulphonamide Therapy, Bull. War Med. **2**:490, 1942.

156. Hall, B. E.; Pfuetze, K.; Hinshaw, H. C., and Feldman, W. H.: Effect of Promin on Blood of Patients with Tuberculosis: Preliminary Report, Proc. Staff Meet., Mayo Clin. **17**:24, 1942.

157. Javert, C. T.: Erythroblastosis Neonatorum: An Obstetrical-Pathological Study of Forty-Seven Cases, Surg., Gynec. & Obst. **74**:1, 1942.

158. Follis, R. H., Jr.; Jackson, D., and Carnes, W. H.: Skeletal Changes Associated with Erythroblastosis Foetalis, J. Pediat. **21**:80, 1942.

striking was a marked increase of density. In all the cases serologic tests for syphilis were negative. Henderson [159] reports 4 cases of severe erythroblastosis foetalis with intrauterine death of the fetus. The findings in this disease and in congenital syphilis are compared. The author points out that the latter condition is likely to die out with successive pregnancies, whereas erythroblastosis tends to become more severe. Attention is drawn to the characteristic change of the placenta in erythroblastosis, consisting in persistence to term of Langhans' layer of cells in the chorionic villi.

In a letter to the editor of the *British Medical Journal* Levy [160] mentions polyostatic fibrous dysplasia, or Allbright's syndrome, as a possible sequel to erythroblastosis foetalis, which he prefers to term "hemolytic disease of the new-born," since neither anemia nor erythroblastosis may be conspicuous. Dizygotic twins suffering with erythroblastosis are reported by Buhler, Seely and McCormick.[161] Their mother was 31 years old. She had been gravid eight times and had been delivered of 5 children, 3 of whom were living. There had been two abortions. The twins died, and necropsies confirmed the diagnosis. The first twin was a stillborn girl. No tests for Rh agglutinin in her blood were made. The second, a boy, lived for sixty hours, and his erythrocytes were shown to be Rh positive. The father's erythrocytes were also Rh positive; the mother's were Rh negative.

The subject of isoimmunization with reference to erythroblastosis foetalis and other manifestations is discussed by Levine.[162] He points out that, unlike the Rh antigen, A and B factors are widespread throughout the tissues, and that consequently isoimmunization of the mother to A and B agglutinins of the fetus with subsequent action of the anti-A and anti-B factors within the fetal tissues may be an important cause of fetal mortality. The author refers to the probable role of isoimmunization in animals and states that concepts of this type of reaction have been formulated and discussed in the older literature but that until now the data have been inconclusive. He considers that the subject merits reopening.

Forty-eight mothers of infants suffering with erythroblastosis were studied by Boorman, Dodd and Mollison [163] with reference to the Rh factor. The erythrocytes of all of the affected babies were Rh positive, the erythrocytes of 46 of the mothers were Rh negative, and in the blood of 44 of the mothers Rh agglutinin was demonstrated. In the 4 mothers without Rh antibodies other group differences were found; for instance, the maternal blood belonged to group O and the fetal blood to group A. In the blood of both members of identical twins Rh agglutinin was detected within twenty-four hours after birth. The authors submit evidence indicating that some cases of "physiological" icterus of the newborn are really instances of mild icterus gravis neonatorum, since weak Rh agglutinin was demonstrated in the blood of some mothers of infants with "physiological" jaundice.

The pathologic examination of 3,000 fetuses and newborn infants revealed erythroblastosis in 120, according to Potter.[164] The blood of 81 of the mothers

159. Henderson, J. L.: Erythroblastosis or Congenital Syphilis? Observations on Erythroblastosis and Its Differential Diagnosis from Congenital Syphilis, J. Obst. & Gynaec. Brit. Emp. **49**:499, 1942.

160. Levy, H.: Erythroblastosis Foetalis, Brit. M. J. **2**:738, 1942.

161. Buhler, V. B.; Seely, C. W., and McCormick, C., Jr.: Erythroblastosis Foetalis in Dizygotic Twins, J. Missouri M. A. **39**:106, 1942.

162. Levine, P.: Erythroblastosis Foetalis and Other Manifestations of Isoimmunization, West. J. Surg. **50**:468, 1942.

163. Boorman, K. E.; Dodd, B. E., and Mollison, P. L.: The Clinical Significance of the Rh Factor, Brit. M. J. **2**:535 and 569, 1942.

164. Potter, E. L.: The Rh Factor in Erythroblastosis, Am. J. Dis. Child. **64**:957 (Nov.) 1942.

of these infants was studied with reference to the presence of Rh agglutinogen in the erythrocytes. Of 50 mothers of infants with the pathologic diagnosis of erythroblastosis foetalis, 86 per cent were found to have blood cells negative for Rh antigen and 14 per cent blood cells positive for this antigen; whereas, of 31 mothers of infants who did not have pathologic evidence of erythroblastosis, 15.5 per cent had blood cells negative for Rh antigen and the remainder blood cells positive for this antigen. Two infants with erythroblastosis foetalis were shown to have Rh negative erythrocytes and 1 father of an affected infant to have Rh negative erythrocytes.

The isoimmunization theory of erythroblastosis foetalis postulates the passage of fetal erythrocytes across the placental barrier into the maternal blood stream. Since this is not a physiologic process, the presence of placental defects as well as an immunologic reaction between maternal antibody and fetal red cells must be assumed in all cases of erythroblastosis. Burnham [165] submits the hypothesis that breaks in the integrity of the fetal circulation through the placenta are dependent on maternal deficiency of vitamin C, and that, therefore, the administration of vitamin C during pregnancy may be of prophylactic value in cases in which there is a history of erythroblastosis or unexplained fetal deaths. The author presents some clinical evidence in support of this theory.

Differences in specificity and in sensitivity between human anti-Rh serums were noted by Davidsohn and Toharsky.[166] They advocate the use of at least three such serums in testing for the Rh factor. There are also antigenic variations of the Rh factors from human sources, and definite differences in this respect between man and Macacus rhesus monkeys with Rh-positive tests. Taylor and his associates [167] found that the weakly Rh-positive erythrocytes failed to agglutinate with undiluted anti-Rh serum obtained from the mother of an infant who died of erythroblastosis, but that agglutination took place when the serum was suitably diluted. They therefore advocate that a titration method be used before reaching the conclusion that anti-Rh factor is not present in a serum.

A discussion of the role of Rh isoimmunization in the genesis of erythroblastosis foetalis and certain transfusion reactions is given by Aagaard,[168] who reports 2 such reactions in women recipients. In an article on hemolytic transfusion reactions, Wiener [169] reports the case of a 16 month old child in whom serum autoagglutinins were demonstrated which retained their activity at refrigerator, room or body temperature. According to the author, a similar case has been observed by Kracke but has not been reported.

Franklin [170] reports the case of an infant in whom sulfhemoglobinemia developed spontaneously about twelve days after birth and was followed by severe anemia without erythroblastosis, jaundice or splenomegaly. The sulfhemoglobinemia and anemia responded to blood transfusions, but the child subsequently died of emaciation and bronchopneumonia.

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165. Burnham, L.: Vitamin C Deficiency as a Possible Factor in the Pathogenesis of Erythroblastosis Foetalis, Am. J. Obst. & Gynec. **44**:920, 1942.

166. Davidsohn, I., and Toharsky, B.: The Rh Blood Factor: An Antigenic Analysis, Am. J. Clin. Path. **12**:434, 1943.

167. Taylor, G. L., and others: Optimal Proportions of Antigen and Antibody in Tests for Rh Antibodies, Brit. M. J. **2**:572, 1942.

168. Aagaard, G. M.: Transfusion Reactions and Erythroblastosis Foetalis Caused by the Rh Factor, Minnesota Med. **25**:267, 1942.

169. Wiener, A. S.: Hemolytic Transfusion Reactions: Diagnosis with Special Reference to the Method of Differential Agglutination, Am. J. Clin. Path. **12**:189, 1942.

170. Franklin, A. W.: Sulphæmoglobin (cyth) æmia and Anæmia Neonatorum, Proc. Roy. Soc. Med. **35**:686, 1942.

Sickle Cell Anemia.—Two cases of sickle cell anemia in the white race are reported by Morrison, Samwick and Landsberg.[171] The ancestors of the patients, who were unrelated, were Italian, and their parents were born in Italy and emigrated to the United States. The sickling trait was detected, in each instance, by means of material obtained by splenic puncture. Subsequently, the trait was demonstrated in members of three generations of both families.

A detailed description of the changes in the brain occurring as the result of sickle cell anemia has been published by Wertham, Mitchell and Angrist.[172] Five unselected fatal cases of the disease provided the material for this study. The presence of sickle cells in the tissues was the most conspicuous neuropathic feature. Small necrotic and necrobiotic lesions on a vascular basis were observed, diffusely distributed, but most numerous in the zone between the cortex and the subcortical white matter. In all cases there were hypertrophy and hyperplasia of endothelial and adventitial cells lining the smaller blood vessels, with siderotic pigment appearing both in the adventitial cells and in the intra-adventitial spaces. Generalized hyperemia and constriction of blood vessels were conspicuous. Small hemorrhages and extravasations were prevalent, and larger vascular lesions of uncharacteristic type, including softening and thrombosis, were seen. Intravascular lipoid material, with fat embolism of the capillaries and precapillaries, was observed, together with focal and diffuse changes in the nerve cells in the cortical and subcortical gray structures. In addition, focal areas of demyelination were present in the spinal cord, similar to those seen in subacute combined degeneration.

The case of a Negro woman aged 20 who died with massive cerebral necrosis on the basis of sickle cell anemia is reported by Connell.[173] According to the author, this is the fifth case to be reported. He states that his patient presented the most extensive cerebral necrosis due to sickle cell anemia which has so far been described. Ultimately, the entire left hemisphere became involved, although in view of the history the onset and progress of the condition appeared to have been gradual. The author emphasizes that in this disease it is not anemia but thrombosis which constitutes the most important pathologic process. Such vascular lesions may occur in any organ but are especially common in those with a terminal circulation.

It is well known that cardiac enlargement is a usual finding in patients with sickle cell anemia. Klinefelter[174] confirms this observation on the basis of a study of 12 cases of the disease including postmortem examination in 11 instances. In all of the patients the heart was diffusely enlarged. Usually both a systolic and a diastolic murmur were present, together with a third sound heard at the apex and accentuation of the second pulmonic sound, with a systolic murmur at the base. The author discusses the similarities between rheumatic fever and sickle cell anemia and points out that in the latter condition pain is not confined to the joints and that the therapeutic response to administration of salicylates is not striking. He states that necropsy has never confirmed the concomitance of rheumatic fever and sickle cell anemia. The cardiac changes in the latter disease are

171. Morrison, M.; Samwick, A. A., and Landsberg, E.: Sickle Cell Anemia in the White Race: Report of Two Cases with Diagnosis by Splenic Puncture, Am. J. Dis. Child. **64**:881 (Nov.) 1942.

172. Wertham, F.; Mitchell, N., and Angrist, A.: The Brain in Sickle Cell Anemia, Arch. Neurol. & Psychiat. **47**:752 (May) 1942.

173. Connell, J. H.: Cerebral Necrosis in Sickle Cell Disease, J. A. M. A. **118**:893 (March 14) 1942.

174. Klinefelter, H. F.: The Heart in Sickle Cell Anemia, Am. J. M. Sc. **203**:34, 1942.

believed to be due to long-standing severe anemia, and congestive failure, not responding to digitalis therapy, is common only in the terminal stages of the disease.

The varied types of cutaneous manifestations occurring in sickle cell anemia are described by McGavack and Nussbaum.[175] Of 214 cases observed by the authors, jaundice was present in 204, and ulcers of the extremities, usually on the medial aspect of the leg above the ankle, were found in 55. Other changes included areas of vitiligo, with surrounding zones of increased pigmentation, and subcutaneous nodules which bore a resemblance to the lesions of erythema nodosum.

During a five year period, ending on Nov. 1, 1941, 57,455 Negro males were admitted to the Charity Hospital, New Orleans, according to Getzoff.[176] A diagnosis of sickle cell anemia was made for 65 of them. Sickle cell anemia was not observed in any white patient. In this five year period priapism was noted in 11 Negro males, and in 3 this complication occurred with sickle cell anemia. Priapism in these 3 is explained as due to venous stasis resulting in increased sickling and thrombosis.

The first case of sickle cell anemia to be described in the medical literature of Argentina was reported by Zerbino, Volpe and Norbis.[177] The patient was a 2½ year old Mulatto girl, and the disease was entirely characteristic.

Erythroblastic (Cooley's) Anemia.—The case of a young man 19 years old, of Sicilian origin, with erythroblastic anemia is reported by Smith.[178] The patient had been under observation since the age of 4 and presented all the clinical, hematologic and roentgenologic features of the disease. In childhood he required blood transfusions, but his development to adult life was normal, and he participated in all forms of activity and exhibited no special susceptibility to infections. One sibling also had Cooley's anemia, and the red cells of another sibling and both parents showed abnormalities, including varying numbers of hypochromic macrocytes and basophilic stippling. The erythrocytes of the father and the brother showed increased resistance to hypotonic solutions of sodium chloride, together with abnormal thinness. Such morphologic changes in the erythrocytes indicate, in the author's opinion, that the relatives of their patient were carriers of this disorder. This case was also reported, in less detail, in 1941.

McIntosh and Wood,[179] explaining the development of erythroblastic anemia, exclude on the basis of improbability most types of genetic factors. They believe that the simultaneous inheritance of two dominant and nonlethal genes is compatible with the observed clinical evidence of a 1 : 3 incidence of the disease among siblings.

(To Be Continued)

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175. McGavack, T. H., and Nussbaum, C. C.: Skin Manifestations of Sickle Cell Anemia, Urol. & Cutan. Rev. **46**:194, 1942.

176. Getzoff, P. L.: Priapism and Sickle Cell Anemia: A Report of Three Cases, J. Urol. **48**:407, 1942.

177. Zerbino, V.; Volpe, A., and Norbis, A.: Anemia a células falciformes en una mulatita, Arch. argent. de pediat. **17**:303, 1942.

178. Smith, C. H.: Mediterranean (Cooley's) Anemia in a Youth of Nineteen Years Observed Since Early Childhood: Familial Aspects and Hematologic Features of the "Carrier" or Asymptomatic Case, J. Pediat. **20**:370, 1942.

179. McIntosh, R., and Wood, C. L.: An Inquiry into the Genetic Factor in Cooley's Anemia, Am. J. Dis. Child. **64**:192 (July) 1942.

Correspondence

A RENAL CONCENTRATION TEST USING SOLUTION OF PITUITARY

To the Editor:—I read with great interest the excellent paper of Lieutenant Harry C. Wall entitled "A Renal Concentration Test Using Solution of Pituitary" in the April 1943 issue of the ARCHIVES OF INTERNAL MEDICINE.

I am sure that you and the author will be interested in the fact that in 1921 I published a paper, "Pituitrin zur Nierenfunktionsprüfung" (*Med. Klin.* **17**:871 [July 17] 1921).

As the title implies, I suggested the use of solution of pituitary instead of a period of thirst in order to determine the ability of the kidneys to produce a concentrated urine. I reported 3 cases of impaired renal function in which tests done by means of solution of pituitary gave the same results as tests of concentration done by means of a period of thirst. I am sorry that I have no reprint to send you.

F. BRUNN, M.D., New York.

Book Reviews

Osler's Principles and Practice of Medicine. By Henry A. Christian, A.M., M.D., LL.D., Hon. Sc.D., Hon. F.R.C.P. (Canada), F.A.C.P. Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University; Physician in Chief, Emeritus, Peter Bent Brigham Hospital; Visiting Physician, Beth Israel Hospital, Boston. Pp. 1475. Cloth. Price, $9.50. New York: D. Appleton-Century Company, Inc., 1942.

This is the fourteenth edition of this book and celebrates its fiftieth birthday. A comparison of the first edition with the present one has shown that the original work contains 1,079 pages and the present edition 1,475. It is a tribute to the present author that he has been able to bring the work up to date with the addition of these relatively few pages. One must remember that vitamins, hormones, the types of cardiac arrhythmia and even diphtheria antitoxin, to say nothing of sulfanilamide and its derivatives, were still to be introduced into medicine in 1892. The specific infectious diseases of the first edition have been subdivided into groups according to causative agents: bacteria, viruses, rickettsias, bartonellas, fungi and protozoa. None of the "infectious diseases of doubtful nature" of the first edition are so listed in the present one. These have all been fitted into the proper places. There is, however, a bigger and better list to supply the deficit. These represent only a few of the many changes. Even so, it is surprising how much of the original work could be written almost unchanged into the present one.

The book is, of course, excellent. The background plus the present author would insure this. Much of the material has been rearranged. Among the infectious diseases, typhoid has yielded first place to pneumonia. It is rather surprising that the author has given first place in the book to psychosomatic medicine and functional diseases of the nervous system. There can be no question of the increasing incidence of these disorders, but one wonders whether they should occupy first place in the mind of the student or even first place in a textbook. Perhaps it is a trend of the times.

Brucellosis in Man and Animals. By I. F. Huddleson, D.V.M., Research Professor in Bacteriology, Michigan State College; A. V. Hardy, M.D., Associate Professor of Epidemiology, Columbia University Medical School; J. E. Debono, M.D., Professor of Pharmacology and Therapeutics, Royal University of Malta; Ward Giltner, D.V.M., Professor of Bacteriology, Michigan State College. Revised edition. Price $3.50. Pp. xxii + 379, with 42 illustrations. New York: The Commonwealth Fund, 1943.

The Archives of Internal Medicine has already bowed in a complimentary manner to what might be termed the grandfather and father of this book. For the first edition appeared as a short monograph in 1934 and received a pleasant notice (Arch. Int. Med. **54**:658 [Oct.] 1934), and the second edition, which came out in 1940 as a larger and more comprehensive study, also received a flattering review (ibid. **66**:1358 [Dec.] 1940).

The third edition continues to live up to the standards of its forebears. As one reads the book now, one is struck with the fact that it has been put together by a competent team of experts, each member of which knows so well what he writes that the final result is admirable. Brucellosis is so discussed that the bacteriologist, the pathologist, the veterinarian, the public health official and the clinician can find in the volume what he wishes to learn.

The first edition included a bibliography of one hundred and thirty-eight titles. The third edition refers to four hundred and eighty-five articles. Thus the third edition keeps abreast of the times and continues to make the book an effective aid in helping to control a disease which is becoming increasingly important over the entire world.

A Manual of Pulmonary Tuberculosis and an Atlas of Thoracic Roentgenology. By D. O. N. Lindberg, M.D., Lecturer on Tuberculosis, University of Iowa Medical College. Price $6.50. Pp. xv + 233, with 199 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1943.

The author has divided this book into two parts: The first is a seventy-two page monograph on pulmonary tuberculosis; the second is an atlas of thoracic roentgenology. Each is written briefly and clearly.

At the outset, in the first part of the book, pulmonary tuberculosis is discussed in orthodox fashion by a short description of its pathology and methods of diagnosis. Then

comes a chapter which is of chief interest to the reader who is not an expert roentgenologist. For here is described roentgenologic technic and interpretation of roentgenograms of the chest. Two excellent chapters on the treatment of tuberculosis follow, the first dealing with methods of medical treatment and the second with modern ways of attacking tuberculosis by surgical measures. Finally, a brief chapter discusses control of the disease. The text is accompanied with forty-four excellent charts and photographs which illustrate the pathologic changes in tuberculosis, its method of spread and the mechanical implements used in its diagnosis and treatment. The net result is pleasing.

The second part of the book is an atlas of one hundred and forty-five roentgenograms chosen to illustrate how pulmonary tuberculosis in different forms appears on a roentgenogram and how it can be differentiated from some of the more common intrathoracic lesions that so often puzzle every internist. The significance and high points of each illustration are explained in a few words. The roentgenograms have been reproduced with a notable degree of success, so that little in the way of fine detail has been lost.

The total result is a helpful book. Its author deserves hearty congratulations. He has condensed into a surprisingly small volume a comprehensive manual of pulmonary tuberculosis which will be appreciated by medical students, by practitioners and by specialists in the field of pulmonary disease.

Clinical Roentgenology of the Cardiovascular System. By Hugo Roesler, M.D., F.A.C.P., Associate Professor of Roentgenology and Cardiologist, Department of Medicine, Temple University School of Medicine; Cardiologist, Temple University Hospital, Philadelphia. Second edition. Price $7.50. Pp. 480, with 337 figures. Springfield, Ill.: Charles C Thomas, Publisher, 1943.

This monograph is an authoritative presentation of the physiology and pathology of the cardiovascular system. It is viewed from the roentgenologic aspect by a cardiologist with a wealth of clinical experience and material.

The text describes technic, apparatus and findings of the most acceptable methods in roentgenoscopy, fluoroscopy, orthodiagraphy, roentgenography, cinematography, kymography and vasography. Interpretations include etiologic factors and differential diagnoses.

The organization of the subjects is such that reference may readily be made to detail of technical methods; correlation from different aspects; interrelationships of heart, vessels, lungs, diaphragm and the thoracic cage in the dynamics of blood flow and respiration, and discussions of changes in cardiac, concomitant pulmonary, aortic, pericardial, pulmonic and peripheral vascular diseases. Each chapter is replete with excellent illustrations, diagrams, electrocardiograms, medical histories, clinical courses, in many instances covering a long course of years, postmortem data and an extensive bibliography.

The book is invaluable in adding knowledge to those on whom lies the task of diagnosis of cardiovascular diseases.

Blood Groups and Transfusion. By A. S. Wiener, M.D., Serologist and Bacteriologist in the office of the Chief Medical Examiner of New York City. Third Edition. Price $7.50. Pp. xix + 438 with 106 tables and 69 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1943.

The first two editions of this book have already received compliments from the ARCHIVES OF INTERNAL MEDICINE. The first edition was reviewed in the issue of December 1935 (**56**:1298 [Dec.] 1935) and the second in the issue of December 1940 (**66**:1360 [Dec.] 1940). The third edition, too, without question deserves praise.

As was said in the review of the first edition, the book brings together practically everything that is known about blood groups. It does this in a readable, scholarly way. To make the subject matter more graphic and readily understandable, it has many good illustrations.

The third edition discusses the Rh factor and its role in erythroblastosis foetalis and transfusion of stored blood and blood substitutes—two subjects not mentioned in the first edition. The book is almost exactly twice as large as it was in the beginning, which seems to indicate that much has been added to the knowledge of blood in eight years. Naturally, the third edition is a better and more comprehensive volume than either of its predecessors, but it continues to hew to the old line in a satisfactory manner.

Dictionary of Bio-Chemistry and Related Subjects. Edited by W. M. Melisoff, Professor of Bio-Chemistry, Brooklyn Polytechnic Institute. Price $7.50. Pp. 579. New York: Philosophical Library, Inc., 1943.

Nowadays the internist hears a good deal of a new kind of language which is likely to be all Greek to him but which his friends who are interested in chemistry or physics speak with fluent glibness. Thus a lexicon of such a new language is bound to be helpful to the casual listener: One can learn a good deal of any tongue by the diligent translation of new words or phrases into one's own vocabulary.

The editors of this dictionary have completed a task for which many members of the medical profession will be grateful. The editorial board is comprised chiefly of a group of distinguished biochemists who have added to their roster an occasional clinician. Between them they have been ingenious enough to complete a readable dictionary, defining in a readily understandable way many of the new words which they use so fluently in connection with their daily work. Usually the various definitions for each word take up a few lines, but occasionally a short article is necessary to explain a word whose meaning cannot be simplified. In such instances a useful bibliography is appended to the article.

The preface states that the dictionary is a pioneering effort in an entirely new field. It is, in fact, sort of a cross between an ordinary dictionary and an encyclopedia. All medical students and a great many physicians will appreciate having placed at their disposal such a useful tool.

Civilian Health in Wartime. Francis R. Dieuaide, M.D., Associate Professor of Medicine, Harvard Medical School and Member of the Staff of the Massachusetts General Hospital. Price, $2.50. Cambridge, Mass.: Harvard University Press, 1942.

The author presents a well written book covering phases of health on which the war will exert an influence. In the first chapter he considers the effect of war on the civilian population and on its mode of life. In the subsequent chapters he discusses these problems in detail, outlining the effects and the methods of prevention. The chapters on nutrition are especially good and timely. A chapter on "The Aging and the Aged" offers an optimistic note for this group. In the final chapters he emphasizes the result of war stress on civilian mental health and morale and discusses how these may be maintained. He discusses these problems from the standpoint of the physician, with a fine interest in public health and social welfare.

The reviewer believes that "Civilian Health in Wartime" will not appeal to the general reader because of its technicalities, but feels that it is worth while reading for the physician, the medical student, the social worker and students in sociology. It would serve well as required reading for any student of social trends.

The entire substance of the book is well handled. Particularly commendable is the author's modern outlook concerning not only medical care but other needs of the community.

La urobilina en el estado normal y patologico. By Marcello Royer. Second edition. Buenos Aires: El Atenéo, 1943.

Well printed, this small volume contains review and original work covering the physiology and pathology of urobilin. Brief, well organized for reference, interesting in the original experiments and studies, the book, alas, definitely puts an end to the hopes of both investigators in clinical laboratories and clinicians that urobilin, so temping to test for, is of any practical clinical diagnostic value.

Medico-Legal Blood Group Determination. By David Harley. Price 2s. 6d. Pp. 119, with 13 figures. London: William Heinemann Medical Books, Inc., New York: Grune & Stratton, Inc., 1943.

This little book covers in a thorough manner the medicolegal aspects of determinations of blood group, especially with reference to questions of disputed paternity, blood stains, etc. Much of the material is highly technical, and it becomes evident that the more esoteric problem of blood typing usually must be dealt with by an expert. There are a bibliography, an index and many illustrative charts and figures.

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